Temperature Post Out-of-hospital Cardiac Arrest - the TOPCAT Study

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i Abstract

Introduction

Out-of-hospital cardiac arrest (OHCA) is a significant cause of death and severe neurological disability in Scotland. Optimal pre-hospital resuscitation is required for the patient to achieve return of spontaneous circulation (ROSC). The only post-ROSC therapy shown to increase survival is mild therapeutic hypothermia (MTH), but its mechanism of action and optimal application are still unknown. The quality of pre-hospital resuscitation in Scotland is unmeasured. The relationship between body temperature post-OHCA, systemic inflammation, markers of brain injury and outcome are still poorly defined. This study examines two aspects of OHCA; firstly, the clinical practice of resuscitation in the pre-hospital and Emergency Department (ED) setting and, secondly, the post-ROSC physiological changes of body temperature, systemic inflammation and serum markers of brain injury.

Methods

Prospective observational study of all OHCA patients admitted to a single centre for a 14-month period (1/08/2008 to 1/02/2010). Oesophageal temperature was measured, blood samples assayed for markers of systemic inflammation (TNF-α, IL-1β, IL-6, IL-8, IL-10, IL-12, elastase, cell surface markers of neutrophil activation) and markers of brain injury (neuron-specific enolase [NSE], S100b, glial fibrillary acidic protein [GFAP]) in the ED and Intensive Care Unit (ICU). Selected patients had pre-hospital temperature monitoring and blood sampling. Routine physiological variables were recorded. Patients who survived to ICU had repeat blood samples taken at 24-,48-,72- and 120-hours post-ROSC. Patients were followed up for 6-months. We conducted qualitative analysis of the effect of having a doctor on-scene at an OHCA and performed a Scottish national survey on the ED management of post-OHCA patients.

Results

236 OHCA patients were included in the study. 161 (68%) were pronounced dead at the scene or in the ED. 75 (32%) were admitted to ICU for cooling; 49 (21%) died in ICU and 27 (11%) survived to hospital discharge. We have characterised the natural progression of core body temperature post-OHCA. Patients who achieved ROSC and had oesophageal temperature measured pre-hospital all had temperatures below normal. Quality of pre-hospital resuscitation performed by ambulance crews was observed to be highly variable.

Standard ED care of post-OHCA patients varied across Scotland. All patients arriving in the ED post-OHCA had a relatively low temperature (34.3°C, 95% CI 34.1-34.5). Patients surviving to hospital discharge were warmer on admission to ICU than patients who died in hospital (35.6°C vs. 34.4°C, $p<0.01$). Patients surviving to hospital discharge also took longer to reach target therapeutic hypothermia level than non-survivors (222 vs. 313 min, $p<0.05$). Cell surface markers of neutrophil activation, IL-6, IL-8, IL-10 and elastase were all significantly raised in the early post-ROSC period. The degree of cytokinaemia at 24-hours was related to survival outcome. In the context of MTH, S100b at 24-hours was superior to NSE and GFAP at predicting in-hospital death following OHCA, with an AUC-ROC of 0.90 (95% CI 0.82-0.98).

Conclusions

The quality of pre-hospital and in-hospital resuscitation in Scotland is variable. Both pre-hospital and ED management of OHCA patients varied on a local and national scale.

Following OHCA all patients have oesophageal temperatures below normal in the pre-hospital phase and on arrival in the ED. Patients who achieve ROSC following OHCA and survive to hospital discharge are warmer on arrival in ICU and take longer to reach target MTH temperatures compared to patients who die in hospital.

A systemic inflammatory response occurs earlier in the post-ROSC phase than previously anticipated. S100b is a more reliable predictor of outcome following OHCA than NSE or GFAP. The mechanisms of action underlying changes in oesophageal temperature and survival from OHCA remain unclear. This study adds to the information around oesophageal temperature post-OHCA and MTH further studies are warranted to clarify the mechanism of action of MTH post-OHCA and the role of inflammatory response in determining survival.

ii Declaration

This thesis is submitted to the University of Edinburgh for the degree of Doctor of Medicine. The work herein was composed by Dr Richard Lyon and carried out under the supervision of Dr Gareth Clegg, Clinical Senior Lecturer and Honorary Consultant in Emergency Medicine, Edinburgh, UK, and Professor Peter Andrews, Professor of Anaesthesia, Critical Care and Pain Medicine, Western General Hospital, Edinburgh, and was undertaken within the Department of Emergency Medicine, Royal Infirmary of Edinburgh.

The work was carried out with the help of a research group, however their contributions are indicated and except where stated, this thesis is the result of my own work and in accordance with the University of Edinburgh regulations governing the degree of Doctor of Medicine. This thesis has not been submitted in whole or in part for any other degree or diploma at this or any other university.

Date: 14th October 2010 Signed:

During the research period the following papers were published:

1. Oesophageal temperature after out-of-hospital cardiac arrest: an observational study.
   Lyon RM, Richardson S, Hay AW, Andrews PJD, Robertson CE, Clegg G
   Resuscitation 2010; 81: 867-871

2. Therapeutic hypothermia in the emergency department following out-of-hospital cardiac arrest – a review
   Lyon RM, Robertson CE, Clegg GR
   Emergency Medicine Journal 2010; 27:418-423

3. Issues around conducting pre-hospital research on out-of-hospital cardiac arrest.
   Lyon RM, Egan G, Gowens P, Andrews P, Clegg G
   Emergency Medicine Journal 2010; 27: 637-638

4. Early in-hospital management of out-of-hospital cardiac arrest: a national survey.
   Lyon RM, Shepherd J, Clegg GR
   European Journal of Emergency Medicine 2011; 18:102-104

5. Back to basics: Improving survival from out-of-hospital cardiac arrest
   Lyon RM, Sinclair N, Henderson C
   Journal of Paramedic Practice 2010; 2(10): 456-460

6. Resuscitation quality assurance for out-of-hospital cardiac arrest: setting up an ambulance defibrillator network
   Lyon RM, Clarke S, Gowens P, Egan G, Clegg GR
   Resuscitation 2010; 81: 1726-8

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During the research period the following presentations were given at conferences:

1. Back to Basics - ECG impedance analysis for CPR quality control and feedback after out-of-hospital cardiac arrest: a pilot study
   13th International Conference on Emergency Medicine, Singapore 2010

2. Temperature post out-of-hospital cardiac arrest – the TOPCAT study
   Inaugural Scientific Meeting of Scottish Board of the College of Emergency Medicine, 2010

3. Early in-hospital physiology of out-of-hospital cardiac arrest
   Inaugural Scientific Meeting of Scottish Board of the College of Emergency Medicine, 2010

4. Scottish Resuscitation Group Annual Conference
   Invited speaker on out-of-hospital cardiac arrest research, 2009

During the research period the following presentations were given at meetings:

1. Scottish Ambulance Service National Clinical Effectiveness Group
   Update on TOPCAT study and CPR in south east Scotland, 2009

2. Faculty of Pre-hospital Care, RCS Edinburgh, Scientific Meeting
   Invited speaker on the TOPCAT study, 2009

The following prizes were gained during the research period:

1. Rod Little Prize for Best Trainee Research Presentation – Back to basics: improving quality of pre-hospital resuscitation
   College of Emergency Medicine Conference, Birmingham, 2010

2. Prize for Best Research Presentation - the TOPCAT study
   Inaugural Scientific Meeting of Scottish Board of the College of Emergency Medicine, 2010

3. Emergency Medicine Journal Prize for Best Research Poster
   Faculty of Pre-Hospital Care Scientific Meeting, Warwick, 2009

4. Alison Gourdie Memorial Prize
   Travel prize to visit resuscitation research centres in Scandinavia & Austria, 2009

5. European Resuscitation Council Young Investigator of the Year 2010 – Runner Up

During the research period the following posters were presented at conferences

1. Temperature post out-of-hospital cardiac arrest – the TOPCAT study
   13th International Conference on Emergency Medicine, Singapore 2010

2. EMS crews' attitudes towards working with pre-hospital medical staff in the field
   13th International Conference on Emergency Medicine, Singapore 2010

iii Summary table of contents

Total thesis word count= 24,008 words (excluding references and appendices)

References. Where more than one publication in the same year, by the same author are cited, "a", "b", "c" are used to differentiate individual papers.

iv Detailed Table of Contents

v List of Tables and Figures

vi List of abbreviations

ASAP	As soon as possible
AUC	Area under curve
CBA	Cytometric bead array
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
ED	Emergency Department
EMDC	Emergency Medical Dispatch Centre
GFAP	Glial fibrillary acidic protein
HNE	Human Neutrophil Elastase
ICU	Intensive Care Unit
IL	Interleukin
MREC	Medical Research Ethics Committee
MTH	Mild therapeutic hypothermia
NSE	Neuron specific enolase
OHCA	Out-of-hospital cardiac arrest
PCI	Percutaneous coronary intervention
PEA	Pulseless electrical activity
RCT	Randomised clinical trials
ROC	Receiver operator characteristic
ROS	Reactive oxygen species
ROSC	Return of spontaneous circulation
SAS	Scottish Ambulance Service
S-100B	Serum protein S-100B
T_{oes}	Oesophageal temperature
T_{targ}	Time from onset of cooling to reaching therapeutic temperature
TTI	Transthoracic impedance
UK	United Kingdom
VF	Ventricular fibrillation
VT	Ventricular tachycardia

vii Dedication

This thesis is dedicated to my family: my mother, Pamela, for her strength beyond words and inspirational determination; my late father, Clive, for providing me with the opportunity to fulfil my life ambition to become an Emergency Doctor; to James and Christopher for their endless support, and to my partner, Caroline, for her love, support and endless patience for the "bat phone" during the many months that it took me to undertake this work.

viii Acknowledgements

The TOPCAT study principal investigators were myself and the following three colleagues to whom I owe many thanks:

Dr Gareth Clegg, Clinical Senior Lecturer and Honorary Consultant in Emergency Medicine, University of Edinburgh, Edinburgh, UK. I owe Gareth thanks for his support in planning and conducting this study, supporting and advising me during my period as a Clinical Research Fellow and for assistance with drafting manuscripts for journal publication.

Prof Peter Andrews, Professor of Anaesthesia, Critical Care and Pain Medicine, Western General Hospital, Edinburgh, UK. Peter was involved in the planning of the TOPCAT study, methodology and drafting manuscripts for journal publication.

Prof Colin Robertson, Professor of Emergency Medicine, Emergency Department, Royal Infirmary of Edinburgh, UK. Colin provided invaluable advice and guidance during the study period.

I am indebted to my colleagues – doctors, nurses and students – in the Emergency Department and Intensive Care Units of the Edinburgh Royal Infirmary, without whom I would not have been able to collect research samples and data.

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I acknowledge statistical advice from Ms Catriona Graham, Lead Statistician, Epidemiology and Statistics Core, Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh.

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Chapter 1

Introduction, Background and Literature Review

1.1 The problem of OHCA

Out-of-hospital cardiac arrest (OHCA) is a leading cause of morbidity and mortality in the developed world. Resuscitation is attempted in 66 per 100,000 population across Europe every year (Atwood, 2005). Of those that survive to leave hospital, over 50% are left with permanent neurological sequalae (de Vreede-Swagemakers, 1997). The only clinical intervention in the post resuscitation phase of OHCA shown to decrease mortality and improve neurological outcome is mild therapeutic hypothermia (MTH) (Bernard, 2002; The Hypothermia after Cardiac Arrest Study Group, 2002).

1.2 The 3-phase model of cardiac arrest

It has been suggested that survival from OHCA depends on the implementation of therapeutic measures in a temporal sequence (Weisfeldt, 2002). In the early phase (0-4 minutes) following loss of cardiac output, defibrillation is required to achieve return of spontaneous circulation (ROSC). Maintenance of circulation by cardiopulmonary resuscitation (CPR) is required if the period of cardiac arrest is prolonged (4-10 minutes) and ROSC is not achieved. Resuscitation must then deal with the metabolic consequences of prolonged cardiac arrest and MTH is thought to be pivotal during this phase.

With the advent of therapeutic hypothermia as a new therapeutic option following OHCA, many ambulance services and receiving hospitals have been eager to implement cooling. This may have detracted from the other important elements of resuscitation – prompt defibrillation and quality cardiopulmonary resuscitation (Olasveengen, 2007). "Hands-on-the-chest" time has been shown to be closely linked to survival from OHCA (Berg, 2001).

1.3 The History of Mild Therapeutic Hypothermia

Descriptions of hypothermia being used to treat patients have been written for over 200 years (Varon, 1991). There are documented cases of Hippocrates and several Greek physicians

experimenting with its use. A Russian method of resuscitation in 1803 described OHCA patients being covered in snow, in the hope this would achieve ROSC (Liss, 1986).

Therapeutic hypothermia was used by French physicians in the Napoleonic wars following traumatic amputations and in 1912 by Temple Fay in a bid to slow the rate of cancer cell multiplication. The first reported use of therapeutic hypothermia for neuroprotection of the ischemic brain was described in 1950 by Bigelow and McBirnie (Bigelow, 1954). Using a canine model, core body temperature was reduced to <25°C during cardiac surgery. The area of neurological injury contained less oedema, less haemorrhage and a reduced inflammatory response.

Benson and Yates described the first use of therapeutic hypothermia outside the operating theatre in 1959 in Baltimore where they noted improvement in survival in patients treated with hypothermia following OHCA (Benson, 1959). Twelve patients post-OHCA were treated with therapeutic hypothermia using a cooling blanket, six of whom survived without residual neurological deficit.

Despite the possibility of therapeutic hypothermia showing promise in improving the poor survival rates from OHCA, it was largely abandoned until the 1990s, mainly due to is significant clinical side effects. Clinical trials had been complicated by the effects of total body cooling, including arrhthymias, shivering, vasospasm, coagulopathy and increased rates of infection. At this time it was felt the moderate (28-32°C) was required to achieve effective brain protection.

The concept of preserving the brain in the field, protecting it from hypoxia until the patient could be transported to hospital for spontaneous circulation to be restored or placed on cardiopulmonary bypass was first suggested by Peter Safar in 1984 (Safar, 1990; Safar, 2000). In the 1990s, a number of encouraging animal studies showed benefit and several pilot human studies were conducted (Bernard, 1997; Yanagawa, 1998). In 2002, two randomised trials demonstrated the benefit of cooling survivors of witnessed OHCA who had ventricular fibrillation (VF) as the presenting rhythm (Bernard, 2002; The Hypothermia after Cardiac Arrest Study Group, 2002). This lead to the International Liaison Committee on Resuscitation, the American Heart Association and the European Resuscitation Council recommending MTH in the management of unconscious patients following OHCA (Nolan, 2003; Nolan, 2008). Despite these recommendations, the use of MTH is not yet routine

(Merchant, 2006b). Since 2002, further trials have explored the use of MTH for non-VF OHCA, traumatic cardiac arrests and in paediatric patients.

1.4 Background to thesis

In this first chapter, the background of this thesis will be discussed. Current management of adult OHCA patients and the available evidence for the use of MTH will be presented. The scientific rationale for cooling, possible mechanisms of action and role of biomarkers post-OHCA will be explored. We will highlight the areas of therapeutic hypothermia that remain under investigation.

The optimum timing of initiation, method and duration of cooling are unclear (Nolan, 2005) and calls have been made to address these questions in order to improve hypothermia as a therapy. Animal research suggests cooling early, either pre-ROSC or immediately post-ROSC, is associated with improved neurological outcome (Sterz, 1991; Wang, 2010; Zhao, 2008). Several human studies have also demonstrated benefit from early cooling (Castren, 2010). Some human studies show that delayed cooling also yields favourable results (The Hypothermia after Cardiac Arrest Study Group, 2002; Wolff, 2009; Zhao, 2008).

Both invasive and non-invasive cooling methods have been developed and whole-body and brain-only cooling methods have been trialled (Bernard, 2002; Castren, 2010). The majority of cooling techniques have been trialled in critical care settings with few methods specifically evaluated in the Emergency Department (ED) (Holzer, 2008b). Whilst MTH initiated in the ED may reduce the time taken to reach target temperature, pre-hospital cooling poses logistical and technical challenges. Patients arriving at hospital after OHCA may require in-hospital transfer for imaging or cardiac intervention prior to Intensive Care Unit (ICU) admission. Cooling techniques intended for early deployment must therefore combine efficacy with ease of use.

While some ambulance services and Emergency Departments have adopted MTH as a routine therapy for patients post OHCA, it is unclear whether the available evidence supports this practice.

1.5 Literature Review of the efficacy of therapeutic hypothermia post-OHCA in the pre-hospital and Emergency Department setting

A literature review was performed by a single investigator (RL). All short-listed studies were assessed for quality and to ensure the inclusion criteria were met. Search terms included "therapeutic hypothermia", "hypothermia", "cardiac arrest", "heart arrest", "out-of-hospital cardiac arrest", and "cardiopulmonary resuscitation". Outcome parameters included in-hospital mortality, 6-month mortality and favourable neurological outcome (defined as independent living) within 6 months.

Inclusion criteria were studies commencing cooling early post-ROSC. For human studies we included those commencing cooling pre-hospital or in the ED. For animal studies we included cooling before, during or immediately after cardiac arrest. Specific exclusion criteria included non-cardiac arrest conditions e.g. myocardial infarction, cerebrovascular accident and traumatic brain injury. In contrast to previous published systematic reviews (Cheung, 2006; Holzer, 2005), we specifically examined MTH use in the pre-hospital and ED setting. We found the number of randomised controlled trials (RCTs) on the use of MTH post-OHCA to be small, therefore all randomised trials were screened for inclusion, regardless of the timing of initiation of cooling.

We included literature searches from Ovid Medline 1950-2010, the Cochrane Library, EMBASE 1988-2010, Google scholar and citation tracking. The search sought to identify studies that evaluated the use of MTH post-OHCA using the search criteria above. Finally, a Web of Science citation search was performed on all included studies. Reference lists of all available primary studies and review articles were obtained to identify potentially relevant citations. Previously published systematic review articles were sought, looking for particular relevance to using MTH in the pre-hospital and ED setting. After a generalised search, limits were applied for "trials".

Human trials were assessed using the Jadad system (Jadad, 1996) to assess internal validity. This allows a measure of comparison of quality between trials. 1062 papers were screened for inclusion. These were subdivided in animal studies, non-randomised studies, randomised trials and systematic reviews. Two systematic reviews and five randomised clinical trials were identified. Five animal trials comparing timing of cooling initiation were included.

1.6 Animal Studies of therapeutic hypothermia

The first animal studies using hypothermia after cardiac arrest were reported in the 1950s. In the early 1960s, Peter Safar observed that dogs that were mildly hypothermic at the initiation of experimental cardiac arrest had a better neurological outcome than dogs that were normothermic (Safar, 1988).

A summary of selected animal studies are shown in Table 1.1. These particularly relate to early cooling and the potential effect this may have on outcome.

Table 1.1. Animal models of therapeutic hypothermia after out-of-hospital cardiac arrest

Study (Year)	Animal Model	Cooling method + target temp.	Duration of cooling	Outcome	Comments
Sterz 1991	30 dogs. 10 minute VF arrest model. RCT of cooling during CPR vs. early post ROSC cooling vs. normothermia	Cooling externally 34°C	20 hours	Improved neurological outcome when cooling started during CPR or immediately after ROSC.	External CPR and resuscitation drugs used as per human practice.
Kuboyama (Kuboyama, 1993) 1993	22 dogs, induced VF for 12.5mins. Prospective RCT of normothermia vs. immediate hypothermia vs. delayed (15 mins after reperfusion) cooling	Cooling on bypass 34°C	1 hour	Immediate cooling showed trend towards better functional outcome compared to delayed cooling and associated with lower histologic damage scores	Functional outcome did not reach statistical significance.
Nozari (Nozari, 2004) 2004	27 dogs. VF cardiac arrest model with 40 minutes no-flow time. RCT of normothermia vs. mild hypothermia vs. moderate hypothermia	Cooling with venovenous extracorporeal shunt - 34°C	12 hours	Mild or moderate hypothermia during prolonged CPR improved survival and functional outcome.	Invasive techniques used, not easily applicable to humans.
Abella (Abella, 2004) 2004	30 mice. Potassium-induced arrest. Prospective RCT of intra-arrest cooling vs. delayed (20 min) post-arrest cooling vs. normothermia	Cooling with cooling blanket 30°C	1 hour	Intra-arrest cooling showed better survival to 72h than delayed cooling or normothermia	Results statistically significant. Only asystolic arrests.
Zhao 2008	45 mice. Potassium-induced cardiac arrest for 8 mins. Prospective RCT of normothermia vs. intra-arrest cooling vs. prolonged resuscitation (9.5 mins) to initiate cooling	Cooling with cooling blanket 30°C	90 seconds	Animals treated with hypothermia, even in prolonged ischaemia group showed improved survival compared to normothermic controls. Haemodynamic variables also improved.	Results statistically significant. Early intra-arrest cooling possible only in pre-hospital setting. Intra-arrest cooling may be useful for haemodynamic resuscitation.

The discovery of the neuroprotective effects of mild to moderate hypothermia led to the investigation of resuscitative hypothermia in several animal models. Dogs treated with immediate mild (34°C) or moderate (30°C) hypothermia showed improved functional and histological outcome. Dogs treated with deep hypothermia (15°C), however, showed no improvement in neurological function and had more severe cerebral histological changes compared to mild or moderate hypothermia groups (Sterz, 1991; Weinrauch, 1992). In the same model, delaying the onset of cooling until 15 minutes post reperfusion was not associated with the same improvement in functional outcome but did improve histologic damage compared to normothermic controls. MTH was not associated with any significant side effects in these studies.

More recently a trend towards better outcomes after earlier initiation of therapeutic hypothermia (<15 minutes post ROSC) has been demonstrated (Abella, 2004; Kuboyama, 1993). Kuboyama and colleagues demonstrated that survival without neurological deficit can still be achieved after 40 minutes of VF cardiac arrest in dogs when intra-arrest hypothermia is instigated using cold intravascular fluids. However, a delay in cooling after the induction of VF was associated with an increased mortality and poorer neurological outcomes (Kuboyama, 1993). Nozari showed that early intra-arrest cooling in dogs with 60 minutes of VF resulted in a favourable neurological outcome (Nozari, 2004). But when cooling was delayed until 20 minutes after onset of VF, 7 of 8 dogs did not survive. Abella and colleagues showed that mice cooled 20-minutes after cardiac arrest showed a higher mortality than mice cooled just prior to resuscitation from an 8-minute period of cardiac arrest (Abella, 2004). Zhao demonstrated in a randomised, controlled, murine model that delaying resuscitation to institute therapeutic hypothermia still resulted in a favourable neurological outcome (Zhao, 2008).

The animal studies reviewed suggest that cooling should commence with a minimum of delay after cardiac arrest and should continue for at least 24 hours to confer lasting neuroprotection. Recent studies have demonstrated that intra-arrest cooling may improve early resuscitation outcome (Castren, 2010; Wang, 2010) and randomised studies are currently being undertaken in this field.

1.7 Non-randomised human trials of therapeutic hypothermia

The first reported human studies using therapeutic hypothermia were reported in 1958 (WILLIAMS, Jr., 1958). Since then over 20 non-randomized studies have been published.

The target temperature has consistently been 32°-34°C using a variety of cooling techniques. Reported favourable neurological outcome rates vary from 25 to 68%. A summary of non-randomised trials is shown in Table 1.2.

Table 1.2. Non-randomised human studies of therapeutic hypothermia initially pre-hospital or in Emergency Department after cardiac arrest

Study	Year	Initial cardiac rhythm	Cooling method + target temperature	T_{targ} (min)	Duration of cooling	Outcomes
Bernard (n=22)	1997	Any	Ice packs 33°C	74	12h	No significant side effects. Increased survival and better neurological outcome compared to historical controls.
Yanagawa (n=13)	1998	Any	Cooling blanket 33-34°C	414	48h	Cooling associated with increased rates of pneumonia. Higher survival and recovery rates in hypothermia group.
Zeiner (n=27)	2000	Any	Cold air	276	>24 hours	No major complications in first 24 hours. Mild resuscitative hypothermia shown to be safe and feasible.
Felberg (n=9)	2001	Any	Cooling blanket	378	24 hours	No major complications. Cooling methods found to be slow and imprecise. Favourable neurological outcome demonstrated.
Bernard (n=22)	2003	Any	Cold fluids (30ml/kg 4°C Ringers), ice	ASAP		Rapid drop in core body temperature from 35.5 to 33.8°C, improved BP and renal function. No cases of pulmonary oedema.
Kim (n=17)	2005	Any	Cold fluids (2L 4°C Saline)	ASAP	24h	Fluid infusion did not alter ejection fraction, central venous pressure or pulmonary pressures.
Busch (n=27)	2006	Any	Sports ice packs and water soaked towels placed pre-hospital	450	12-24 hours	Cooling rates found to be slow. Higher in-hospital survival rates in cooled patients.
Merchant (n=32)	2006	Any	Cooling blanket	360	12-24 hours	Majority of cases showed unintentional overcooling to <32° C
Kliegel (n=20)	2007	Any	Cold fluids (4°C saline 30ml-kg-hr)	60	24 hours	Majority reached <34°C in <60 mins

In 1997, Bernard and colleagues conducted a pilot study comparing patients treated with MTH, induced by the application of ice packs, with normothermic controls. They demonstrated improved outcome in the treatment group, without significant complications (Bernard, 1997). Yanagawa cooled 13 patients who had survived initial resuscitation (Yanagawa, 1998). Cooling to 33°C commenced on arrival to the Emergency Department (time to target temperature of 5.5 hours post ROSC) and was maintained for 48 hours before slowly rewarming at 1°C per day.

Further studies adopted progressively more sophisticated means of inducing therapeutic hypothermia. A study using cold air surface cooling in the Emergency Department by Zeiner and colleagues was successful in lowering core body temperature (Zeiner, 2000). Despite non-significant results, these studies supported the evidence that MTH was a safe clinical intervention and could improve outcome after OHCA.

Cooling modalities are summarised in Table 1.3. Methods of initiating pre-hospital cooling have been investigated, with cold fluids and ice packs being the modalities of choice (Busch, 2006; Kim, 2005). Other methods of cooling, including body surface cooling with ice and cold blankets, helmet devices, endovascular cooling catheters, haemofiltration and coronary bypass have been studied (Hachimi-Idrissi, 2001; Haugk, 2007; Holzer, 2008a). None of these combine efficacy with ease of use. A key finding is infusion of up to 2 litres of cold (4°C) intravenous fluid (0.9% saline or Ringer's lactate) in the immediate post-ROSC phase is an effective and safe method of cooling and is not associated with significant complications or cardiovascular instability (Kim, 2005). Whatever the cooling technique employed, the degree of hypothermia induced is important and Merchant and colleagues have demonstrated that overcooling is a significant risk and careful core body temperature monitoring is mandatory (Merchant, 2006a). The risks of overcooling include infection, coagulopathy and cardiac arrhythmias (Polderman, 2008a).

Table 1.3. Methods of inducing/maintaining therapeutic hypothermia

Invasive techniques	Non-invasive techniques
Cold intravenous fluid infusion	Ice packs
Extracorporeal cooling blood circuit Cardiopulmonary bypass Femoral-carotid bypass	Cooling blankets (water / air filled) Cooling helmets (water / air filled)
Lavage Nasal / nasogastric / rectal / peritoneal Ice slush	Cold water immersion Self adhesive cooling pads
Endovascular cooling catheter	Intra-nasal cooling devices (eg Rhinochill)

1.8 Randomised trials of therapeutic hypothermia

Five randomised clinical trials of therapeutic hypothermia post out-of-hospital cardiac arrest have been published (Bernard, 2002; Hachimi-Idrissi, 2001; Kim, 2007; Laurent, 2005; The Hypothermia after Cardiac Arrest Study Group, 2002). These are summarised in Table 1.4. The first clinical trial of therapeutic hypothermia, published in 2001 (Hachimi-Idrissi, 2001), enrolled 30 patients following OHCA with asystole or pulseless electrical activity as initial cardiac rhythm. Sixteen patients were cooled to 34°C for a maximum of 4 hours with a helmet cooling device and then allowed to passively rewarm. Two of the patients treated with MTH survived with a favourable neurological outcome compared to no patients in the normothermia group.

In 2002, two prospective, randomised controlled trials of MTH in the post-resuscitation management of witnessed OHCA were published (Bernard, 2002; The Hypothermia after Cardiac Arrest Study Group, 2002). Both of these studies recruited a highly selected cohort of patients, with 92% of patients initially assessed for eligibility excluded.

Recruitment criteria for both trials were similar and included ROSC in patients who remained intubated and ventilated after OHCA due to VF of presumed cardiac aetiology. The European trial cooled 136 patients to a core temperature of 32° to 34°C using a mattress cover that delivered cold air. The aim was to reach target temperature within 4 hours of ROSC, maintain it for 24 hours and then allow passive rewarming to occur. The study showed NNT=6 (relative risk [RR] 1.40, 95% CI 1.08-1.81) for a favourable neurological

outcome when MTH was used. The overall mortality at 6 months was reduced from 55% in the normothermia group to 41% in the MTH group, NNT=7 (RR 0.74, 95% CI 0.58-0.95).

In the Australian study, cooling was initiated pre-hospital by applying ice packs to the head and torso. The target temperature (33°C) was maintained for 12 hours post-hospital admission before patients were actively rewarmed after 18 hours. 43 patients were cooled, 21 (49%) had a favourable neurological outcome of living at home or within a rehabilitation facility compared to the control group (RR 1.85, 95% CI 0.97-3.49, NNT=4). Mortality was reduced from 68% to 51% in the hypothermia group (RR 0.76, 95% CI 0.52-1.10, NNT=6). These findings led to the European Resuscitation Council, in association with the International Liaison Committee on Resuscitation and the American Heart Association, recommending MTH as standard therapy for OHCA victims that achieve ROSC following a VF arrest (Nolan, 2003).

A randomised trial (Laurent, 2005) of inducing MTH by isovolumic haemofiltration in patients post-OHCA showed an increased survival benefit, but it was unclear whether this was conferred by the hypothermic or filtration processes. This technique is not suitable for use in the emergency and pre-hospital environment.

A recent clinical pilot study explored the benefit of cooling patients immediately after OHCA using intravenous cold saline administered by paramedics in the field (Kim, 2007). An infusion of 500 to 2000ml of 0.9% saline at 4°C was administered. Subsequent in-hospital cooling was at the discretion of the attending physician. 63 patients were treated with pre-hospital hypothermia. Only 78% of patients in the hypothermia group received further cooling. Pre-hospital cooling led to a significantly lower temperature on arrival to hospital (34.7C vs. 35.7C, $p<0.0001$). There was no significant difference in survival to hospital discharge in the hypothermia vs. normothermia groups (33% vs. 29%, $p=0.70$). Subgroup analysis of patients with VF as the initial cardiac rhythm showed a trend towards increased survival to hospital discharge but there was a trend towards increased mortality in the cooling group where the initial cardiac rhythm was PEA or asystole.

Pre-hospital, intra-arrest cooling using intra-nasal vapour is a novel concept that an early study has shown to be safe and effective (Castren, 2010). Selective brain cooling with this method negates then need for intravenous volume loading and further studies are currently being conducted to evaluate this method in comparison to other cooling modalities.

Table 1.4. Randomised clinical trials of mild therapeutic hypothermia for out-of-hospital cardiac arrest.

Study (nr of patients)	Initial cardiac rhythm	Cooling method + target temp	T_{targ}	Duration of cooling	Patients	Survival to hospital discharge	Favourable neurological outcome	Comments
Hachimi-Idrissi, 2001 (n=30)	Asystole or PEA	Cooling helmet. 34°C	3h post ROSC	4 hours	16 – MTH 14- normothermia	MTH – 2/16 (13%) Normothermia – 0/14	Same as survival rate	Results NS (P=0.49)
Bernard 2002 (n=77)	VF or pulseless VT	Ice packs 33°C	2h post ROSC	12 hours	43 – MTH 34 - normothermia	MTH – 21/43 (49%) Normothermia – 9/34(26%)	Same as survival rate. OR for favourable neuro. recovery 5.25 (95%CI 1.47-18.79)	Results significant (P=0.046)
HACA 2002 (n=275)	VF or pulseless VT	Cooling mattress /ice packs 32-34°C	6h after initiating cooling	24 hours	136 – MTH 137 – normothermia		MTH – 75/1236 (55%) NT – 54/137 (39%)	Trend towards high infection rate in hypothermia group but benefit deemed to outweigh risk.
Laurent 2005 (n=61)	VF or asystole	Cooling of the substitution fluid on haemofiltraiton		24 hours	Haemofiltration – 20 HF + hypothermia – 22	OR for survival 4.4 (95% CI 1.1-16.6)		Results from haemofiltration alone were similar to haemofiltration with MTH. Haemofiltration is not practical for use within ED
Kim 2007 (n=125)	All rhythms after non-traumatic OHCA	Infusion of up to 2L 4°C saline pre-hospital	Variable	Variable	63 – cooling 62 - normothermia	NS		Significantly lower ED arrival temp in group treated with cold IV fluid. Trend towards worse survival in non-VF patients treated with MHT.
Castren 2010 (n=200)	All witnessed	Rhinochill intra-nasal cooling to <34°C	Faster when commenced with Rhinochill	24 hours	96 – pre-hospital Rhinochill 104 – in-hospital cooling	NS	NS	Rhinochill intra-nasal pre-hospital cooling is safe and feasible and may confer increased survival benefit in select patients

1.9 Systematic reviews of therapeutic hypothermia initiated in the pre-hospital or Emergency Department phase following OHCA

Cheung et al reviewed the data from 4 RCTs in 2006, representing 436 patients (Cheung, 2006). Inclusion criteria were adults with primary OHCA who remained comatose after ROSC. The clinical trials ranged from score 1 to 3 on the Jadad scale and A-C on the Cochrane grade score. The combined data showed that MTH deceased in-hospital mortality (RR 0.75, 95% CI 0.62-0.84). The review concluded MTH had an NNT of 5 to improve neurological outcome and an NNT of 7 to save a life. However, the review failed to draw conclusions on the optimum cooling method, rate or exact duration of cooling. No evidence of treatment-limiting side effects was reported.

A meta-analysis (Holzer, 2005) of 3 trials of witnessed OHCA patients with VF as the presenting rhythm has shown that patients treated with hypothermia (32-34°C for 12-24 hours) show an increased rate of survival with favourable neurological outcome (RR 1.68, 95% CI 1.29-2.07). The calculated 95% confidence interval for the number needed to treat to result in a patient being discharged from hospital with a favourable neurological outcome ranged from 4 to 13.

1.10 Clinical application of therapeutic hypothermia

There is strong evidence to support the use of MTH in comatose patients after witnessed OHCA whose initial cardiac rhythm was VF. There is less evidence supporting MTH use in other presenting cardiac rhythms and further studies are required. Despite animal studies demonstrating the benefit of immediate cooling, either during CPR or immediately post ROSC (Abella, 2004; Kuboyama, 1993; Zhao, 2008), there is only limited existing evidence from human studies supporting early cooling (Castren, 2010; Wolff, 2009). Practically, initiating cooling in the pre-hospital environment is challenging, however several studies have shown that initiating cooling in the ED is feasible and effective (Bernard, 2003a; Kim, 2005; Kliegel, 2007). Different techniques for initiating and maintaining MTH are shown in Table 1.3. The use of ice packs is a simple, but relatively slow, means of cooling. A bolus of cold intravenous fluids combines efficacy with ease of use but the potential cardiac effects of intravascular volume loading are under debate. Intravenous fluids can be stored in a refrigerator within the ED and administered to post-OHCA patients shortly after arrival in hospital. Initiating cooling in the ED is likely to shorten the time-to-target temperature time, particularly if the patient requires coronary intervention or radiological imaging prior to

Intensive Care Unit admission. Cooling with cold intravenous fluids can continue during transfer or during clinical procedures.

Core body temperature measurement is important during cooling. Ideally, core body temperature needs to be measured using oesophageal, rectal or bladder temperature probes. Tympanic temperature measurement, whilst convenient in the emergency setting, has been shown to be inaccurate in the context of resuscitation (Craig, 2002). In the pre-hospital setting, oesophageal temperature measurement is the most practical.

The three phases of therapeutic hypothermia include induction, maintenance and rewarming. For all phases, accurate core body temperature measurement is essential to ensure accurate cooling and prevent over cooling. For rapid induction, oesophageal or central venous temperature should be measured as probes in the bladder or rectum may not reflect core body temperature accurately (Stone, 1995). Overcooling is common (Merchant, 2006a). After induction, therapeutic hypothermia can be maintained on the ICU with body surface cooling techniques with accurate feedback mechanisms, or invasive, endovascular cooling techniques. In order to prevent shivering, paralysis and sedation are required. The optimum length of time for which MTH should be maintained remains unknown (Gazmuri, 2007; Nolan, 2005) but previous studies have maintenance periods of 12-48 hours (Bernard, 2002; The Hypothermia after Cardiac Arrest Study Group, 2002). The optimum means, whether active or passive, and rate of warming is unknown and further research is required to improve the induction, maintenance and rewarming phases.

1.11 Uptake of therapeutic hypothermia

Despite strong evidence suggesting benefit, uptake of therapeutic hypothermia in routine clinical practice has been slow (Laver, 2006; Merchant, 2006b). Lack of awareness, fear of a novel therapy and unknown side effects as well as lack of equipment have been cited as barriers to therapeutic hypothermia implementation (Varon, 2008). If early achievement of target therapeutic temperature is to be achieved, use of cooling post-OHCA will need to be increased (Abella, 2005).

1.12 Percutaneous coronary intervention and therapeutic hypothermia

Immediate percutaneous coronary intervention (PCI) following OHCA has yet to be widely accepted (Noc, 2008). There is evidence to suggest immediate PCI for OHCA with signs of ST-segment myocardial infarction (STEMI) on the post-ROSC ECG improves outcome, but

evidence for other presentations is limited (Merchant, 2008; Spaulding, 1997). Studies have shown that PCI and initiation of MTH can occur simultaneously (Abella, 2008).

1.13 Summary – Clinical application of mild therapeutic hypothermia following OHCA.

Despite strong evidence suggesting benefit, little is known about the mechanisms of action of MTH as a therapy following OHCA. Possible mechanisms are discussed later in this chapter. Uptake of therapeutic hypothermia in routine clinical practice has been slow (Laver, 2006; Merchant, 2006b). Lack of understanding, awareness, fear of a novel therapy and unknown side effects, as well as lack of equipment, have been cited as barriers to MTH implementation (Acosta, 2008).

1.14 Brain injury after global cerebral ischaemia

Cardiac arrest leads to systemic hypoperfusion and global cerebral ischaemia is thought to result in brain injury. The post-cardiac arrest "syndrome" is complex (Nolan, 2008). Numerous cellular and molecular processes have been described in a complex cascade leading to a final common pathway of ischaemic neuronal injury. Animals models of cerebral ischaemia have been developed to investigate target-specific cytoprotective strategies (Bhardwaj, 2003). Global cerebral ischaemia involves decreased cerebral blood flow across the entire brain and results in a predictable pattern of neuronal, histologic injury, leading to selective cell ischaemic necrosis (Pulsinelli, 1985). If ROSC is achieved, cerebral blood flow is restored but secondary brain injury can occur from influx of neutrophils, reactive oxygen species, cerebral oedema and haemorrhage. Even after normalisation of blood flow, there is continued tissue injury, driven mainly by oxygen free radicals in a reperfusion syndrome thought to last hours to days. These detrimental post-ischaemic effects are exacerbated when the patient's temperature rises above 37°C (Alzaga, 2006).

1.15 Models of global cerebral ischaemia

Both small (mouse, rat, gerbil) animal and large animal (rabbit, dog, pig) models of global cerebral ischaemia have been developed. In the larger animals methods include ventricular fibrillation and aortic occlusion. In these models, specific neuronal cells appear susceptible to injury. CA1 pyramidal neurons in the hippocampus appear most susceptible to injury after 3-5 minutes of ischaemia. Medium-sized neurons of the striatum appear more resistant to injury, surviving for 15-20 minutes of ischaemia (Koehler, 1985). Following ROSC,

differences in irreversible neuronal injury is seen. In medium-sized neurons of the striatum, neuronal injury is observed within 3 hours following ROSC, but delayed to 48-72 hours in CA1 hippocampal neurons, a finding known as "delayed neuronal death" (Koehler RC, 1996).

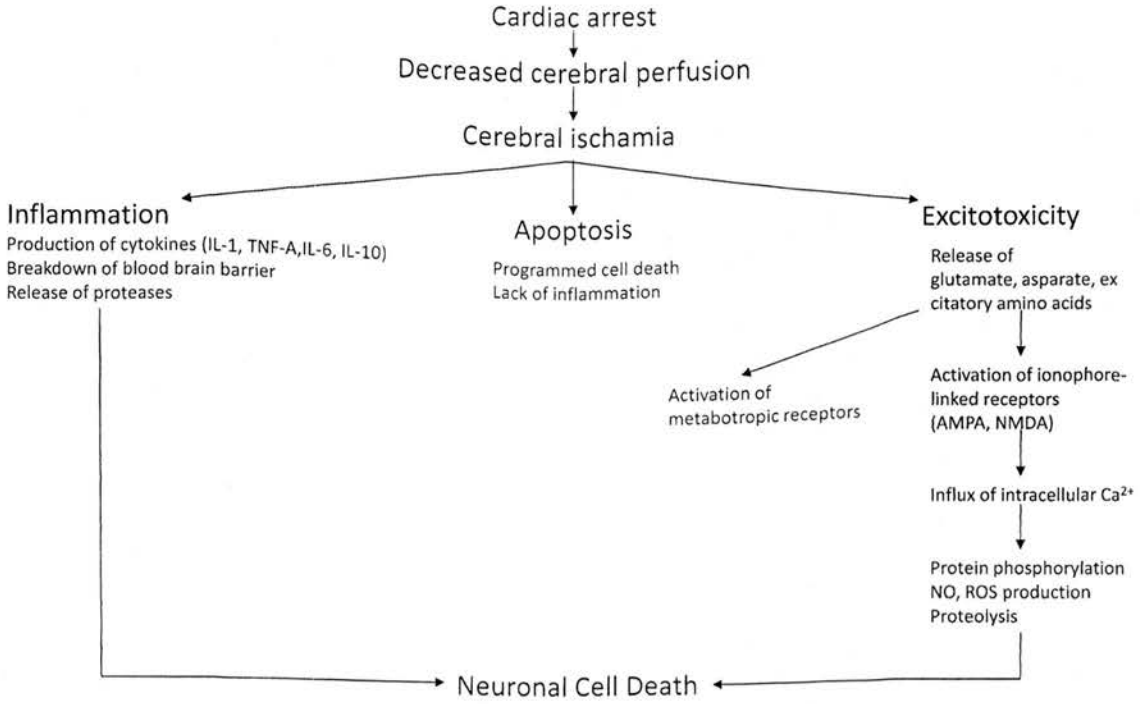
1.16 Components of the post-resuscitation syndrome – neuronal cell injury

Distinct modes of cell death exist. Neuronal cell death is known to occur by two distinct processes. Apoptosis is "programmed" cell death with the self-destruction of damaged cells without injury to surrounding tissues. Necrosis is uncontrolled cell death with the release of cell contents and the potential for damage to surrounding tissues. Although microscopically distinct, apoptosis and necrosis coexist in a spatial distribution within ischaemic neuronal tissue (Koehler RC, 1996). Neurons in the ischaemic core become necrotic and neurons in the penumbra become apoptotic. The duration and severity of the ischaemic insult also influences the mode of neuronal cell death. Neuronal cell necrosis is thought to occur as a result of an excitotoxic cascade triggered by exposure to excitatory amino acids. A common pathway leading to neuronal cell apoptosis has yet to be identified but a mitochondrial-dependent "intrinsic" pathway and receptor-mediated "extrinsic" pathway have been described (Sugawara, 2004).

There are different causes of neuronal cell death. Excitotoxic brain injury occurs when neurotransmitters, such as glutamate and asparate, are released in abundance from neurons. In a healthy, adult brain, extracellular glutamate is cleared by rapid uptake (Globus, 1995). When energy stores are depleted, such as in cerebral hypoxia, cellular depolarisation leads to glutamate being released into the extracellular compartment. Coupled with impaired glutamate uptake, this leads to an increase in intracellular Ca^{2+} (Benveniste, 1984). An increase in intracellular Ca^{2+} leads to lethal intracellular derangements. Glutamate activates three major families of ionophore-linked receptors (N-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], and kainate) and metabotropic receptors that activate second messengers (Sommer, 1992). In vitro studies have shown that glutamate toxicity occurs in an early, rapid NMDA-mediated cascade and a slowly triggered AMPA/kainate pathway. Reactive oxygen species and nitric oxide have also been implicated in neuronal cell damage following cerebral ischaemia.

A summary of the mechanisms of neuronal cell death following cerebral ischaemia is shown in Figure 1.1.

Figure 1.1 Mechanisms of neuronal cell death following cerebral ischaemia



1.17 Systemic injury pro-inflammatory cytokines

Systemic ischaemia and reperfusion injury in OHCA patients results in an acute inflammatory response, characterised by local and systemic production of inflammatory cytokines, including interleukins (IL-1, IL-6, IL-8, IL-10, IL-12) and tumour necrosis factor alpha (Meybohm, 2010a). Inflammatory cytokines are released by ischaemic neurons and glial cells, which generate release of adhesion molecules in the cerebral vasculature, breakdown of the blood-brain barrier, culminating in cerebral oedema (Danton, 2003). Pro-inflammatory cytokines are associated with activated neutrophils that can infiltrate into the interstitium and lead to visceral and cell damage. The pathophysiological role of inflammatory cytokines has been investigated in septic shock (Bone, 1996) and to a lesser degree following ROSC in OHCA patients. Highly significant correlations between pro-inflammatory cytokines and mortality in patients with burns, trauma and sepsis have been reported (Casey, 1993; Svoboda, 1994). Indeed, the post-ROSC phase of OHCA has been described as a severe sepsis-like syndrome with associated pro-inflammatory cytokines and

adhesion molecules, serum endotoxin and dysregulation of cytokine production by neutrophils (Adrie, 2004). The post-ROSC reperfusion syndrome is thought to last for hours, if not days after circulation is restored (Adrie, 2004).

The effect of MTH on pro-inflammatory cytokines in OHCA patients remains under investigation. Several inflammatory cytokines have been shown to predict outcome in animal models of OHCA (Sipos, 2010) but their role in humans is still under investigation. A greater understanding of reperfusion injury after ROSC could, in future, allow more targeted therapy, such as administration of antibodies to specific elements of the inflammatory response (Shyu, 1997) and has been described in animal models (Sekido, 1993).

Previous studies have shown IL-8 and TNF-α to rise following OHCA, to reach a peak 12 and 6 hours post-OHCA respectively with higher levels being associated with an increased early death rate (Ito, 2001). Marked complement and neutrophil activation has been demonstrated in post-ROSC OHCA patients (Adrie, 2004).

IL-1 is known to be detrimental to ischaemic brain injury (Oto, 2008) but the role of IL-6, a pro-inflammatory cytokine, and IL-10, an anti-inflammatory cytokine, are unclear in this context. TNF-α appears to contribute to ischaemic tolerance (Ginis, 2002), as well as propagating ischaemic brain injury (Bruce, 1996). Limited studies have shown that MTH modulated serum pro-inflammatory cytokine levels, with both up and down regulation being observed in different cytokines (Diestel, 2008; Fries, 2009). This study aims to investigate key components of the inflammatory response of OHCA. A summary of cytokines commonly investigated in OHCA is shown in Table 1.5.

Table 1.5. Characteristics of inflammatory cytokines commonly measured post-OHCA

Cytokine	Production site	Action
IL-1b (Bensi, 1987; March, 1985)	Activated macrophages	Pro-inflammatory, involved in cell proliferation, differentiation and apoptosis.
IL-6 (Kishimoto, 1995; Smolen, 2006)	T-cells and macrophages	Both pro- and anti-inflammatory. Crosses blood-brain barrier, acts on hypothalamus influencing body temperature. Inhibits production of TNF-α, IL-1 and IL-10
IL-8 (Baggiolini, 1992)	Macrophages, epithelial cells	Potent chemokine in inflammatory response.
IL-10 (Moore, 2001; Pestka, 2004)	Monocytes and lymphocytes	Down regulates Th1 cytokines, MHC class II antigens
TNF-α (Locksley, 2001)	Mainly macrophages but also lymphoid cells, mast cells, cardiac myocytes and neuronal tissue.	Regulates immune cells, induces apoptotic cell dath.

1.18 Leucocytes post-OHCA

Leucocytes have been implicated in the reperfusion injury following OHCA. Polymorphonuclear neutrophils have been shown to significantly raised in the hours following ROSC (Adrie, 2004; Bottiger, 2002). Leucocyte activation, adherence and sticking is thought to block vessels in the microcirculation (Schmid-Schonbein, 1993). The effect of neutrophil activation in the post-ROSC phase remains under investigation but few studies have examined neutrophil activation post-OHCA in the context of MTH. Neutrophils in the circulation exist in a quiescent state, however on stimulation with endogenous molecules, such as interleukin-8, or exogenous ones, they enter an activated state. This state is characterised by conformational and functional changes, and can be determined from the expression of certain surface markers. Neutrophils contribute to tissue injury by releasing cytotoxic and pro-inflammatory immune mediators.

We chose to measure Human Neutrophil Elastase and several neutrophil cell surface markers (CD11b, CD62L, CD64) as measures of neutrophil activation.

CD11b is a marker of neutrophil activation (Berger, 1984). CD11b has a variety of functions including binding to C3b which is opsonises phagocytic targets and so triggering phagocytosis (Brekke, 2007). It is also an integrin, and so is involved in cellular adhesion and migration (Springer, 1995).

CD62L (also known as L-selectin) is involved in the adhesion of neutrophils to endothelial surfaces prior to transmigration (Simon, 2000). In contrast to CD11b, CD62L is shed from the surface of the neutrophil during in-vitro activation. The picture in-vivo is less clear with groups reporting a diversity of responses, including both up and down regulation of surface expression (Cocks, 1998). However soluble CD62L can be found in increased concentrations in plasma following activation, in other conditions such as sepsis, even if cell surface expression also increases.

CD64 (also known as FcγI) is a receptor for the Fc portion of IgG antibodies, and is involved in mediating cellular responses to IgG-opsonised targets including phagocytosis (van Spriel, 1999). It is generally found at very low levels on neutrophils, in contrast to monocytes which express it highly. However on profound activation it is upregulated on neutrophils, and has been postulated as a marker for severe inflammatory diseases such as sepsis (Layseca-Espinosa, 2002).

As well as cell surface markers, there are neutrophil components released into the plasma on activation. One of these is the enzyme Human Neutrophil Elastase (HNE), which is a proteolytic enzyme involved in the destruction of dead tissue as well as non-oxygen dependent killing of microbes. HNE is released when activated neutrophils degranulate (Faymonville, 1991).

1.19 Markers of neurological injury

Many patients suffer severe neurological injury after OHCA. Strategies are needed to determine as early and accurately as possible, which patients will have a poor neurological outcome (Wijdicks, 2006). Accurate early prognostication is useful for selecting patients for advanced, novel therapies, limiting critical care interventions, rationalising therapy and informing relatives. Several prognostic markers of neurological injury following OHCA

have been investigated but none found to be reliable enough to use in the clinical setting (Shinozaki, 2009a). In particular, neuron specific enolase (NSE) and S-100B have been widely studied. NSE is the neuronal form of the cytoplasmic enzyme enolase. It is a dimeric enzyme (gamma-gamma) with a biological half-life of 24 hours. NSE is mainly found in neurons and neuroendocrine cells (Marangos, 1987). Homodimer S-100B is a calcium binding protein regulating neuronal differentiation, growth and apoptosis. It has a half life of two hours and is mainly found in glial and Schwann cells (Korfias, 2006).

NSE and S-100B have been studied extensively but the majority of the studies were conducted before the widespread adoption of MTH (Meynaar, 2003; Reisinger, 2007; Schoerkhuber, 1999; Shinozaki, 2009b). A subgroup analysis of the Hypothermia after Cardiac Arrest trial, showed a marked reduction in the efficacy of NSE as a predictive marker when measured in cooled OHCA patients (Tiainen, 2003). The effect of MTH on serum markers of brain injury is not known. Sampling time points for both serum biomarkers have not been uniform and the definition of poor outcome ill-defined. Direct comparison between studies is therefore difficult.

Multiple logistic regression analyses on mortality have found NSE and S-100B to be superior to clinical predictors, however the ideal cut-off values and sampling time points have yet to be determined (Shinozaki, 2009b). Few studies have attempted to measure serum biomarkers in the immediate pre-hospital post-ROSC phase of OHCA. There is evidence that NSE is useful as a prognostic marker when MTH is used, but only at 48 hours after ICU admission (Meynaar, 2003; Oksanen, 2009). However, in the same study, a rise in NSE levels was associated with poor neurological outcome at 6 months post OHCA (Oksanen, 2009). MTH has been associated with a decrease in NSE, but not S-100B levels in the 48 hours post-OHCA (Tiainen, 2003).

There have been calls to analyse the time-course of serum S-100B and NSE after CPR, especially in the context of MTH (Sunde, 2009), to offer a reliable indication of what is occurring within the brain following ROSC (Hijdra, 2007). This study investigates the time course of NSE and S-100B from the earliest possible time point, in the context the MTH.

Glial fibrillary acidic protein (GFAP) is a filament protein found in astrocytes and ependymal cells of the central nervous system (Hayashida, 2010). GFAP is involved with many cellular functioning processes, such as cell structure and movement, cell

communication and the functioning of the blood brain barrier. GFAP has been shown to be a highly specific biomarker for traumatic brain injury (Honda, 2010; Pelinka, 2004), and ischaemic stroke (Foerch, 2006).

Previous studies have shown varying results of the ability of GFAP to predict neurological outcome following OHCA (Hayashida, 2010; Kaneko, 2009).

1.20 The role of temperature in the development of brain injury post-OHCA

The roles both brain and systemic body temperature play in neurological outcome following OHCA remain under investigation (Acosta, 2008). Animal models of both focal and global cerebral ischaemia have shown the importance of temperature on determining functional and histological outcome (Busto, 1987). Following an ischaemic insult, cerebral hyperthermia leads to increased microvascular injury (Hajat, 2000), cerebral oedema and the conversion of selective neuronal necrosis to infarction, resulting in increased mortality (Busto, 1987). The rise in core body temperature observed following experimental models of cerebral ischaemia is presumed to be a consequence of brain injury, possibly mediated by an inflammatory response (Zhao, 1994). The precise mechanisms of action of hypothermia for neurological protection are largely unknown (Polderman, 2008a).

1.21 Physiology of temperature regulation and hypothermia induction

Normal human body temperature is strictly regulated and maintained at a set point of 36.6±0.4°C. The set point can be adjusted and minimal variations in temperature occur during the course of each day (Hasan, 2010). Central body temperature is thought to be under hypothalamic control. Body temperature is regulated by limiting the blood supply to peripheries through vasodilation and vasoconstriction. Heat loss from the peripheries is dependent on skin perfusion and sweat production (evaporation). Heat loss can also occur by convection, conduction and radiation. The amount of heat loss is influenced by the temperature gradient, exposed surface and thermal conductivities. At rest under normal circumstances, 50-70% of body heat loss in awake patients will occur through radiation (Polderman, 2009). In unconscious patients in the supine position, most heat loss will occur through radiation and convection (Laupland, 2009). Cooling of patients leads to immediate physiological responses to counteract the disturbance in homeostasis. Vasoconstriction limits heat loss through the skin and sympathetic tone increases to maximise central perfusion. The

capacity and effectiveness to control body temperature decrease with age. During cardiac arrest, lack of circulation and vasoactive tone lead to profound heat loss from the body, although the exact rate and distribution of heat loss following OHCA is unknown.

1.22 The mechanisms of action of mild therapeutic hypothermia

Despite widespread interest in therapeutic hypothermia, little is known the mechanism by which MTH confers benefit, including its cellular and molecular effects (Hansen, 1994). MTH is thought to improve survival from OHCA, provide neuroprotection and possibly increase the likelihood of ROSC when commenced intra-arrest. The mechanism of action resulting in these three effects may be similar or different. The early assumption was that hypothermia conferred survival benefit and neuroprotection mainly by slowing cerebral metabolism and decreasing oxygen demand. Cerebral oxygen consumption, glucose utilisation and lactate concentration are dependent on temperature (Yenari MA, 2005). Hypothermia has been shown to reduce cerebral metabolism by reducing all of these parameters. Metabolism is reduced by 5-7% for each °C reduction in core body temperature (Small, 1999). Therapeutic hypothermia is now thought to exert its effect through several mechanisms (Polderman, 2008b). Animal experiments have shown that the degree of neuroprotection is similar when either mild or deep hypothermia is used, an effect not explained by metabolism reduction alone (Polderman, 2008b). Also, hypothermia appears to confer neuroprotection even when initiated several hours after the initial injury (The Hypothermia after Cardiac Arrest Study Group, 2002).

1.23 Protective effects of mild therapeutic hypothermia

As discussed, hypothermia reduces cerebral metabolism, reducing oxygen and glucose requirements and can limit the reperfusion injury following ROSC. Mild to moderate hypothermia (temperature target of 32-34C) causes cerebral vasoconstriction, reducing cerebral blood flow (Bernard, 2003b). This decreases intracranial pressure and may act as an anti-convulsant (Bernard, 1997).

MTH has effects on the cardiovascular system. Heart rate is decreased and systemic vascular resistance increases (Bernard, 2003b). MTH decreases cardiac output by approximately 7% for each 1°C decrease in core body temperature, whilst stroke volume and mean arterial pressure are maintained.

Patients undergoing MTH have increased diuresis as cooling increases renal blood flow (Zeiner, 2004). There is increased uptake of potassium inside the cells, leading to hypokalaemia (Koht, 1983). Similarly, hypothermia decreases phosphate concentrations.

MTH is not without side-effects. Coagulation is known to be affected, prolonging bleeding time through effects on platelet function and prolongation of prothrombin and partial thromboplastin times (Zeiner, 2000). Hypothermia has been associated with an increased susceptibility to infection, particularly pneumonia (Bernard, 2003b).

Hypothermia may mitigate or block the pro-inflammatory response and production of pro-inflammatory cytokines following ischaemia, although the precise mechanism and which cytokines are affected remain unknown (Diestel, 2008; Fries, 2009).

1.24 Neurological effects of mild therapeutic hypothermia

Injured brains can have areas with 2-3°C higher temperatures than surrounding areas (Zhao, 1994). Injured brain cells can lead to hyperthermia, which is known to propagate neurological injury (Saini, 2009). Hypothermia of 32-34°C can mitigate this effect (Minamisawa, 1990). Hypothermia is thought to improve ion homeostasis, limiting the detrimental effect of glutamate accumulation and Ca^{2+} influx into cells (Polderman, 2008a). Permeability of cellular membranes is reduced, decreasing leakage with associated improvements in cell function and cellular homeostasis, including decreasing intracellular acidosis. Cerebral ischaemia can lead to disruption of the blood-brain barrier and the vascular wall. Hypothermia can moderate this disruption, limiting cerebral oedema (Fischer, 1999). Production of reactive oxygen species (ROS), such as superoxide, peroxynitrite, hydrogen peroxide and hydroxyl radicals is common after ischaemia. Hypothermia is able to block production of ROS (Hashimoto, 2003; Kil, 1996).

1.25 Summary of introduction

MTH has been shown to influence outcome from OHCA in three ways. Firstly, it improves survival (Bernard, 2002; The Hypothermia after Cardiac Arrest Study Group, 2002). Secondly, it improves neurological outcome (Holzer, 2005). Thirdly, it may increase ROSC when commenced intra-arrest (Castren, 2010; Tsai, 2008; Wang, 2010). Little is known about the mechanisms of action of MTH and what effect cooling during resuscitation has on the body.

Suggested mechanisms of MTH exerting neuroprotection include a decrease in cerebral metabolism, decrease in reactive oxygen species production, decreased cell death mediated through calcium and glutamate release and possible modulation of inflammatory cascades.

MTH may modulate systemic inflammation post-ROSC and reduce multi-organ failure (Qureshi, 2008). MTH may have a protective effect on cardiac function post-OHCA (Yannopoulos, 2009; Yu, 2010). MTH, when commenced intra-arrest, may increase the likelihood of ROSC, possibly via sympathetic nervous system stimulation.

Chapter 2

Study Aims and Objectives

2.1 Aims

The aims of the TOPCAT study followed two distinct strands. Firstly, the clinical resuscitation of OHCA patients in Scotland and secondly, physiological changes occurring post-OHCA.

Core body temperature is important after OHCA. The progression of core body temperature after out-of-hospital cardiac arrest and its relation to systemic inflammation and markers of brain injury remains under investigation.

It was the intention to examine core body temperature immediately after OHCA and characterise any relationships to markers of systemic inflammation and brain injury.

The primary aim of this study was therefore:

1. To describe the natural pattern of change in core body temperature after OHCA.
2. Establish any relationship between core body temperature, markers if systemic inflammation (IL-1, IL-6, IL-8, IL-10, IL-12), brain injury (NSE, S100b) and outcome following OHCA.

Secondary aims were:

OHCA clinical management in Scotland

- To review the literature to establish current optimal management of OHCA patients in the ED.
- To establish current practice of ED management of OHCA in Scotland.
- To investigate whether improved research-based guidelines on the management of OHCA patients are required in Scotland.
- To determine whether the presence of a doctor at the scene of OHCA is beneficial.

- To assess ambulance crews' attitudes towards a doctor attending the scene of OHCA.

Physiology post-OHCA

- To enrol 36 patients in the pre-hospital setting and determine core body temperature post-OHCA in the pre-hospital phase.

- To enrol a total of 250 OHCA patients and gather prospective data on core body temperature, markers of systemic inflammation and brain injury post OHCA on arrival in the ED.

- To continuously record body temperature on patients surviving to admission to the ICU and establish whether initial body temperature is related to time-to-reach target temperature, survival to hospital discharge, neurological outcome and best neurological performance within 6 months of OHCA.

- To determine the relationship between core body temperature on arrival in the ED and brain injury markers taken.

- To determine the relationship between core body temperature on arrival in the ED and markers of systemic inflammation.

- To determine the pattern of change of brain injury and systemic inflammation markers in the first 5 days post-OHCA.

- To determine the predictive value of brain injury markers in determining outcome from OHCA in patients receiving therapeutic hypothermia.

2.2 Hypotheses

- Patients post-OHCA are not normothermic in the pre-hospital and ED phases of resuscitation.

- There is an association between core body temperature post-OHCA and outcome.

- Markers of systemic inflammation (IL-1, IL-6, IL-8, IL-10, IL-12) are significantly raised in the hours to days post-ROSC following OHCA.

- Markers of systemic inflammation are significantly higher in OHCA patients who do not survive compared to those who survive to hospital discharge.

- There is a correlation between core body temperature in the early phase post-OHCA and markers of systemic inflammation.

- Markers of brain injury (NSE/S100b) can be used to predict outcome in the context of therapeutic hypothermia.

- Having a doctor on-scene of an OHCA has no impact on patient care or outcome.

Chapter 3

Main Study Methodology

3.1 Setting

The study area covered the Lothians region of south east Scotland, with a population of approximately 500,000. OHCA patients are attended by crews from the Scottish Ambulance Service. The majority (>95%) who are not pronounced dead at scene are transported to the Royal Infirmary of Edinburgh with the remainder being transported to the Western General Hospital, Edinburgh. We only included patients admitted to a single centre – the Royal Infirmary of Edinburgh.

3.2 Study Design

The study was designed as a prospective observational study, called the "Temperature Post Cardiac Arrest" - "TOPCAT" study.

3.3 Patient selection

The Lothians has approximately 450-500 OHCA per annum (Heartstart, 2005). In a 1-year period from 2005-6 the ED of the Royal Infirmary of Edinburgh received 218 patients post OHCA. Of these, 50 patients achieved ROSC and survived to be admitted to hospital (Easterford, 2006). The overall survival-to-discharge rate for OHCA in the Edinburgh area has historically been consistent with that published for other urban centres at around 4%.

3.4 Study period

The TOPCAT study commenced on the 1st August 2008 and data collection ceased on 28th February 2010 (total study period: 19 months). The study ran continuously although patients recruited into the pre-hospital subgroup (see below) were only recruited when the research doctor was available.

3.5 Sample size

We estimated the ED of the Royal Infirmary of Edinburgh would receive approximately 200 patients post OHCA per year. We predicted a recruitment rate of 80% based on our

experience of previous studies on critically ill patients in our unit. Over a 19-month period we would expect to recruit 240-270 patients, with 75 patients expected to survive to reach admission to hospital.

3.6 Inclusion and exclusion criteria

The inclusion criteria for the TOPCAT study were defined as follows:

- aged 16 years or over
- attending the ED RIE following OHCA
- intubated pre-hospital or on arrival to the ED
- OHCA of presumed non-traumatic aetiology

The exclusion criteria were

- age <16 years
- patient not requiring endotracheal intubation
- OHCA of traumatic aetiology
- Pregnancy

3.7 Patient demographics and data collection

All patients taken to the ED post-OHCA have data collected by the Scottish Ambulance Service in the standard Utstein format (Jacobs, 2004). On arrival in the Emergency Department, the OHCA patient was managed according to standard Advanced Life Support guidelines. Patients were recruited into the study at the discretion of the attending Emergency Doctor. The patient was assigned a study number and a standard data collection form completed. The data collection form is shown in Appendix II – Data Collection Form. All data was pseudo-anonymised.

3.8 Core body temperature measurement

Core body temperature monitoring commenced on arrival in the ED. Oesophageal temperature (T_{oes}) monitoring is the most practical means of accurately measuring core body temperature during a resuscitation attempt (Sterz, 2003). An oesophageal temperature probe was marked at 15cm from the tip and inserted via the nostril or mouth as soon as was practical during resuscitation. The thermometer tip was therefore 15cm from the nostril and the position confirmed by laryngoscopy. The probe was linked to a digital recording thermometer (DataTherm II, RG Medical Diagnostics, USA) with oesophageal temperature

recorded every 10 minutes to 0.1°C accuracy. Oesophageal temperature recording continued for a 24-hour period for patients surviving to ICU admission. The temperature trace was downloaded onto a research computer using a direct USB connection and proprietary software (RG Medical Diagnostics Ltd). We recorded the pattern of change in oesophageal temperature from either the pre-hospital, see below, or ED phase of the OHCA patient's journey until target temperature ($T_{targ.}$ <34°C) was reached after cooling was commenced in the ICU. Time taken to reach $T_{targ.}$ after ROSC was recorded, together with time to admission to the ED and ICU and the time active cooling was commenced. Ordinarily in the Royal Infirmary of Edinburgh, therapeutic hypothermia is initiated on the ICU. Body surface cooling (Arctic Sun, Medivance Ltd) is used with automatic temperature feedback control. In a small proportion of cases cooling is commenced in the ED by placing ice packs on the patient.

3.9 Missing Data

We anticipated that, despite frequent reminders, oesophageal temperature monitoring and blood sampling would not be undertaken in a proportion of eligible patients. Where possible, the remainder of blood samples taken for clinical use were obtained and stored for research purposes. In cases where oesophageal temperature monitoring was not undertaken, the ICU clinical chart was obtained and hourly oesophageal temperatures recorded for routine clinical observation noted. All data, including incomplete sets was used for descriptive analysis.

3.10 Blood sampling, storage and assay

On arrival in the Emergency Department, three tubes of blood were taken from the patient for research purposes. Two serum gel tubes were filled with approximately 5ml each of patient blood and one EDTA plasma tube was filled with 5ml of blood. The samples were immediately centrifuged (either in the hospital laboratory or in the ED) at 3200rpm for 10 minutes. The samples were stored at 4°C for a maximum of 48 hours before being aliquotted into 2ml sterile containers and frozen at -80°C in the Queen's Medical Research Institute, Edinburgh, before batch analysis.

Patients surviving to reach admission to the ICU had follow-up blood samples taken at 24, 48 and 72 hours post-arrival in the ED. For patients who survived, a blood sample was taken at 5 days post-admission. Blood samples were processed in an identical manner to those from the ED.

3.11 Human inflammation assay

Human inflammatory markers were analysed using flow cytometry. Flow cytometry is an analysis tool that detects and count antibodies attached to cells using laser excitation. The BD™ Cytometric Bead Array (CBA) uses the sensitivity of amplified fluorescence detection by flow cytometry to measure soluble analytes in a particle-based immunoassay. Each bead in a BD CBA kit provides a capture surface for a specific protein and is analogous Multiplexing is the simultaneous assay of many analytes in a single sample. We used the BD™ Cytometric Bead Array (CBA) to quantitatively measure TNF-α, IL-1β, IL-6, IL-8, IL-10 and IL12p70. The full protocol for analysis of serum inflammatory markers is given in Appendix III – Laboratory protocols. Cell surface markers of neutrophil activation were measured using flow cytometry. The protocol for measuring neutrophil cell surface markers is given in Appendix III – Laboratory protocols. Blood samples were taken from 16 adult, healthy volunteers to act as control samples.

3.12 Brain injury markers assay

We used an automated analyser (Diasorin Liaison) to quantify serum levels of NSE and S-100b.

The method of quantitative determination of NSE and S100 is a sandwich chemiluminescence immunoassay. A specific mouse monoclonal antibody is coated on the magnetic particles (solid phase); another monoclonal antibody is linked to an isoluminol derivative (isoluminol-antibody conjugate). During the incubation, NSE and S100 present in the TOPCAT samples, bind to the solid phase monoclonal antibody and subsequently the antibody conjugate reacts with NSE/S100 already bound to the solid phase. After incubation, the unbound material is removed with a wash cycle. Subsequently, the starter reagents are added and a flash chemiluminescence reaction is thus induced. The light signal, and hence the amount of isoluminol-antibody conjugate, is measured by a photomultiplier as relative light units and is indicative of NSE/S100 concentration in the samples. No control samples were used as the normal serum levels of NSE and S100b are thought to be negligible (Oksanen, 2009).

To measure serum GFAP, a proprietary enzyme-linked immunosorbent assay (Biovendor Human GFAP ELISA) was used. A full description of the ELISA is given in Appendix III – Laboratory Protocols.

3.13 Pre-hospital subgroup

A subset of patients had oesophageal temperature measurement and blood samples taken pre-hospital, at the scene of the out-of-hospital cardiac arrest. Pre-hospital patients were only recruited during the research doctor's on-call periods with the Scottish Ambulance Service. The aim was to recruit 2 patients per month into the pre-hospital subgroup, giving a total of 36 during the study period. Clinical care of the patient was always first priority with the research doctor initially assisting the ambulance crew with resuscitation until data sampling was practical.

3.14 Pre-hospital tasking and response

The research doctor (RL) operated approximately a 1:3 on-call with the Scottish Ambulance Service (SAS). RL received formal response driver training from the SAS. The driving course took place over 3 days (August 18-20, 2008). A detailed account of the Response Driver Training is shown in Appendix IV - Response Driving) The research doctor's car was fitted with an Automated Vehicle Locator System, which uses satellite tracking technology to display availability and location in the Emergency Medical Dispatch Centre (EMDC). All EMDC call handlers and dispatchers were made aware of the study by information sheets and posters. The research doctor (RL) visited EMDC on a weekly basis to encourage appropriate tasking.

On receipt of a possible cardiac arrest call an ambulance was immediately dispatched according to local protocol. The research doctor was then contacted on a designated mobile phone and given the location details of the suspected OHCA. The research doctor received training in emergency response driving and had his car fitted with audible and visual warning systems to allow a fast response as shown in Figure 3.1.

Figure 3.1. TOPCAT response car and equipment.

A specific motor insurance policy (Towergate MIA, London) covered emergency response driving. Standard resuscitation equipment, similar to that carried by Scottish Ambulance Service crews, and a defibrillator (supplied by the British Heart Foundation) was carried by the research doctor in case he arrived first on scene. The full list of emergency medical equipment carried by RL is given in Appendix V – Response car equipment.
All SAS crews within the Lothians region were informed about the study by means of email bulletins. At the scene, the research doctor worked with the attending SAS crew, assisting resuscitation where necessary before starting data collection.

All calls attended by the research doctor were logged and data collected on the time of call, location, incident details and interventions performed by the doctor on-scene, including advice given to the attending ambulance crew.

3.15 Pre-hospital data collection

The oesophageal probe was used accordingly to the same protocol described for patients having temperature monitoring commenced in the Emergency Department. Temperature monitoring commenced as soon as practical during resuscitation, often before ROSC. The temperature probe was secured in place for transport to hospital and continued continuously for 24-hours post-hospital admission or until the patient died.

An intravenous cannula was inserted at the scene and blood taken in the same manner as described for the Emergency Department samples. The blood samples were immediately transported back to the hospital for processing and storage as described above.

3.16 Pre-hospital interaction with Ambulance Crews

All calls that RL received from the EMDC were logged. On arrival at the scene of an OHCA, RL would assist the attending ambulance crew if required. A log of all advice given and clinical procedures performed at the OHCA scene was kept. On completion of the episode, the attending ambulance crew were emailed with a request to anonymously complete an online survey (SurveyMonkey Ltd) about their experiences working with a pre-hospital doctor in the field. The survey, with results included, is shown in Appendix VI - Ambulance crew perceptions of a pre-hospital doctor at the scene of out-of-hospital cardiac arrest.

3.17 Ethics Committee Approval

The study received approval from the national Scottish Medical Research Ethics Committee (MREC "A") on 26th June 2008 (Ref 07/MRE00/119).

Lothian Research and Development management approval was also obtained on 26th March 2008 (Ref 2008/R/AE/02).

3.18 Informed consent and information sheets

The patient and family information sheets (Version 1.2, Appendix VII – Information sheets) and patient and family consent forms (Version 1.2, Appendix VIII – consent forms) were also approved by the MREC.

3.19 Endpoint measures

Patients in the pre-hospital subgroup were either pronounced dead at scene or transported to the ED.

Patients arriving at hospital were either declared dead in the ED, admitted to the ICU or had active treatment withdrawn and admitted to a hospital ward for palliation.

Primary endpoint measures were survival to hospital discharge and best cerebral performance category (CPC) achieved within 6 months post OHCA.

Table 3.1 Cerebral Performance Category scoring

CPC 1.
Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.

CPC 2.
Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.

CPC 3.
Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.

CPC 4.
Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.

CPC 5.

Brain death: apnea, areflexia, EEG silence, etc.

3.20 Statistical Analysis

Data were entered into a database (Microsoft Access 2007) and analysed using statistical analysis software (Microsoft Excel 2009, SPSS 16.0).

Continuous data are presented using mean and standard deviation (SD) and interquartile range (IQR), as appropriate; categorical data are presented using absolute frequencies. Comparisons between continuous variables were performed using Student's test or Mann-Whitney U test as appropriate. Categorical data evaluated using chi-square analysis.

Values in the survivor and non-survivor groups were compared at two time points (arrival in the ED and arrival on the ICU) using an unpaired t-test. Statistical significance was taken at the 95% level.

The primary objective of the study is a descriptive analysis so no formal power calculation was performed. We determined the sample size required to enable a linear regression analysis of our data to meet our secondary objectives:

Using the Peduzzi rule ten events per variable would be needed for a linear regression, equating to a minimum of 60 patients who survive to reach hospital admission over the total study period. The Emergency Department of the Royal Infirmary of Edinburgh (RIE) receives approximately 200 patients post OHCA per year. We predicted a recruitment rate of 80% based on our experience of previous studies on critically ill patients in our unit. Over an 18-month period we expected to recruit 261 patients, with 75 patients expected to survive to reach admission to hospital.

A subset of patients was included in the pre-hospital setting. The lead investigator working a 1 in 3 on-call with the Scottish Ambulance Service would expect to attend 6 OHCA per month. The aim was to recruit 36 patients over the study period.

To determine if there is a cut-off point that would allow us to distinguish between those who survive to discharge versus those who die in ICU, receiver operator characteristic (ROC) curves were produced and the area-under-the curve (AUC) calculated.

Univariate and multiple logistic regression analyses were performed.

Statistical advice, supporting and analysis was facilitated by Ms Catriona Graham, Lead Statistician, Epidemiology and Statistics Core, Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh.

Chapter 4

Early In-Hospital Management of Out-of-Hospital Cardiac Arrest in Scotland: A National Survey

4.1 Introduction

Coronary heart disease is responsible for around 110,000 deaths in the United Kingdom every year with 75% due to sudden cardiac death (Atwood, 2005). In Scotland, there are over 3,500 out-of-hospital cardiac arrests (OHCA) annually, with survival to hospital discharge less than 5% (Heartstart Scotland, 2006).

In the pre-hospital phase effective resuscitation is required in order to obtain return of spontaneous circulation (ROSC). The only therapy in the post-ROSC phase of OHCA shown to improve outcome is mild therapeutic hypothermia (MTH) (Hypothermia after cardiac arrest study group 2002b; Bernard, 2002). This study surveys the use of MTH in Emergency Departments (ED) and Intensive Care Units (ICU) across Scotland.

In 2002, two prospective, randomised controlled trials of MTH in the post-resuscitation management of witnessed OHCA were published (Hypothermia after cardiac arrest study group, 2002a; Bernard, 2002). These papers led to the European Resuscitation Council and the International Liaison Committee on Resuscitation recommending MTH as standard therapy for OHCA patients with ventricular fibrillation (VF) as the presenting rhythm who remain comatose post ROSC (Nolan, 2003). Whether MTH may also benefit patients after OHCA with non-VF presenting rhythms is unknown.

There is still uncertainty amongst physicians about using MTH (Abella, 2005). Recent evidence suggests that early achievement of the desired hypothermic temperature is associated with a better neurological outcome. If target temperature is to be achieved early, cooling will need to commence in the pre-hospital or ED phase of the OHCA patient's care.

Primary percutaneous coronary intervention (PCI) can be considered after ROSC in the management of OHCA. PCI is currently regarded as the most effective reperfusion strategy in ST-elevation myocardial infarction (STEMI) (Keeley, 2003). Whether PCI is beneficial in

cases of non-STEMI acute coronary syndrome complicated by cardiac arrest remains under investigation (Anyfantakis, 2009).

We sought to investigate differences in ED and ICU management of OHCA patients in Scotland and to establish the degree of consistency in the use of MTH and PCI in the management of OHCA. We sought to establish possible reasons for variation in clinical practice and barriers to implementation.

4.2 Methods

A national questionnaire survey was conducted of all Emergency Medicine (EM) Consultants, EDs and ICUs in Scotland. Each Consultant was emailed with an invitation to complete a web-based questionnaire. The full survey is shown in Appendix XI – Scottish Emergency Department Survey. All responses were anonymous and participation was voluntary.

A telephone survey was conducted of all Scottish Emergency Departments (n=26) and Intensive Therapy Units (n=22). On receipt of the telephone call, a member of the on-duty medical team was asked to answer the survey questions. Ethical approval was gained from the University of Edinburgh Student Projects Committee.

4.3 Results

113 Emergency Medicine Consultants were identified as working in Scotland. Contact email addresses were available for 87 of these Consultants. 32 (37%) of the contacted EM Consultants completed the survey. All 26 Scottish EDs and 22 ITUs were contacted by telephone. The telephone survey was completed by 19 (73%) EDs and 21 (96%) ICUs.

4.4 Emergency Medicine Consultant views on OHCA management

32 EM Consultants responded to the survey. The majority (27; 84%) felt MTH was effective in the management of OHCA patients and 26 (84%) had experience of using MTH. A large proportion, (29; 91%) of EM Consultants thought MTH should be commenced earlier (pre-hospital or ED setting). 29 (91%) EM Consultants thought it practical to initiate MTH within the ED.

21 (67%) of ED Consultants did not think PCI should be used routinely in the early management of OHCA. The major trigger for PCI referral was reported as an ECG finding of ST segment elevation.

4.5 Emergency Department management of OHCA

7 (47%) EDs had used cooling before, compared to 19 (91%) ICUs. MTH was more commonly initiated in ICU than in the ED. (19 (91%) vs. 7 (37%), $p<0.05$). The majority of EDs (9; 47%) did not routinely initiating cooling. A protocol for MTH was only present in 4 (21%) EDs, as shown in Table 1.

A protocol for primary PCI use following OHCA was available in 10 (53%) EDs. None of the district general hospitals that received patients following OHCA had on-site access to PCI. 59% of university teaching hospitals had on-site access to PCI.

Table 4.1 Emergency Department management of out-of-hospital cardiac arrest (OHCA), (n=19)

Ever used MTH in the ED on a patient post OHCA		
Yes	7	(37%)
No	12	(63%)
Is it practical to initiate MTH within the ED?		
Yes	15	(79%)
No	4	(21%)
Proportion of post OHCA patients who have MTH initiated in the ED		
None	14	(74%)
<10%	3	(16%)
10-25%	1	(5%)
>25%	1	(5%)
ED protocol for MTH use in OHCA patients		
Yes	4	(21%)
No	15	(79%)
Method of initiating MTH (if used)		
Ice packs	4	(21%)
Surface cooling blankets	2	(11%)
Exposure only	1	(5%)
Cold IV fluids	0	(0%)
Reasons for not initiating MTH in ED		
MTH commenced on ICU	8	(42%)
Cooling equipment unavailable	6	(32%)
Insufficient evidence for using cooling	5	(26%)
Protocol in place for PCI following OHCA		
Yes	10	(53%)
No	9	(47%)
What proportion of post-OHCA patients go for PCI from the ED		
None	4	(21%)
<10%	11	(58%)
10-25%	2	(11%)
>25%	0	(0%)
Access to PCI facility from the ED		
On-site	3	(16%)
Off-site	14	(74%)
No	2	(10%)
Availability of PCI facilities		
24 hours a day	11	(58%)
Mon-Fri 0900-1700	5	(26%)
Available on request	3	(16%)

4.6 Intensive Care Unit management of OHCA

The majority of ICUs (19; 91%) had experience of cooling OHCA patients and utilised a protocol (16; 76%), as shown in Table 2. The majority of OHCA patients admitted to ICU were cooled, with MTH being used in over 50% of admitted OHCA patients in 14 (67%) ICUs.

Table 4.2: Intensive Care Unit Management of out-of-hospital cardiac arrest (OHCA), (n=21)

Ever used MTH in the ICU on a patient post OHCA		
Yes	19	(90%)
No	2	(10%)
Proportion of post OHCA patients who have MTH initiated in the ICU		
None	2	(10%)
<10 %	0	(0%)
10-25 %	2	(10%)
>25 %	17	(80%)
ITU protocol for MTH use in OHCA patients		
Yes	17	(81%)
No	4	(19%)
Method of initiating MTH (if used)		
Ice packs	13	(62%)
Surface cooling blankets	14	(67%)
Cold IV fluids	8	(38%)
Wet towels and fanning	5	(24%)
Invasive cooling	2	(10%)
How long are patients cooled on ICU for (if applicable)		
<6 hours	0	(0%)
6-12 hours	1	(5%)
12-24 hours	2	(10%)
24-48 hours	15	(71%)
>48 hours	1	(5%)

4.7 Discussion

We completed a national survey of Scottish EDs, ICUs and EM Consultants. Compared to previously published studies, we have found an increase in the use of MTH in both the ED and ICU setting. A UK survey in 2006 of 98% of all British ICUs found that only 27% had

ever used MTH (Laver, 2006). Our study reports a 90% MTH experience rate which may imply an increase in the use of MTH on the ICU for post-OHCA patients. We found the majority of Scottish ICUs have adopted a cooling protocol but there remains variation in the cooling techniques used and length of time MTH is maintained, perhaps reflecting the lack of clinical evidence in these areas.

The consensus from clinical studies supporting early cooling has led ILCOR to recommend the initiation of MTH as soon after ROSC as possible (Nolan, 2005). If target temperature is to be achieved early, cooling will almost certainly have to be initiated in the pre-hospital or ED phase of an OHCA patient's care. 91% of EM Consultants thought it practical to initiate MTH in the ED. There appears to be a positive attitude towards MTH but our study has demonstrated a discrepancy in best perceived clinical practice and actual delivered treatment.

None of the surveyed university teaching hospitals routinely used MTH in the ED. The barriers to implementation most often cited for non-use of MTH were lack of a cooling protocol, lack of cooling equipment or MTH being initiated in the ICU instead. Studies have previously reported similar reasons to ours for non-adoption of MTH with the most commonly cited reasons being: lack of evidence, lack of a protocol, difficulties in practicality and lack of resources (Abella, 2005; Skulec, 2010). Establishing protocols for MTH use in the ED and heightened awareness could promote the use of cooling in early OHCA management.

Early post-ROSC PCI has also been shown to improve survival when used in patients surviving OHCA. Evidence suggests OHCA STEMI patients are likely to benefit from early PCI (Anyfantakis, 2009). Whether non-STEMI post-OHCA should have PCI remains unknown and further research is warranted in order to ensure intervention occurs in the correct subset of post-OHCA patients. The management of OHCA needs to be co-ordinated on a regional scale in the form of a cardiac network to ensure patients requiring reperfusion intervention are transported to the appropriate centre. In our study, none of the district general hospitals receiving OHCA patients had on-site access to primary PCI. Some hospitals transferred OHCA patients direct for PCI. The early use of PCI has yet to be widely accepted and physicians are still unsure of its place in the management of OHCA.

There are several limitations to this survey. Our low sample size may not reflect the opinions and practice of all physicians in Scotland involved in the care of OHCA patients. The

telephone survey only interrogated one respondent per department and there is no way of confirming the answers being provided.

4.8 Conclusion

The use of MTH in Scottish EDs is low. Use of MTH on ICU is increasing. Few EDs routinely refer OHCA patients for primary PCI and a concerning number of hospitals receiving patients post-OHCA do not have on-site access to primary PCI facilities. Greater understanding of the role of MTH and PCI in the early management of OHCA will promote these promising treatments amongst Emergency and Critical Care physicians.

Chapter 5

Results – Core body temperature

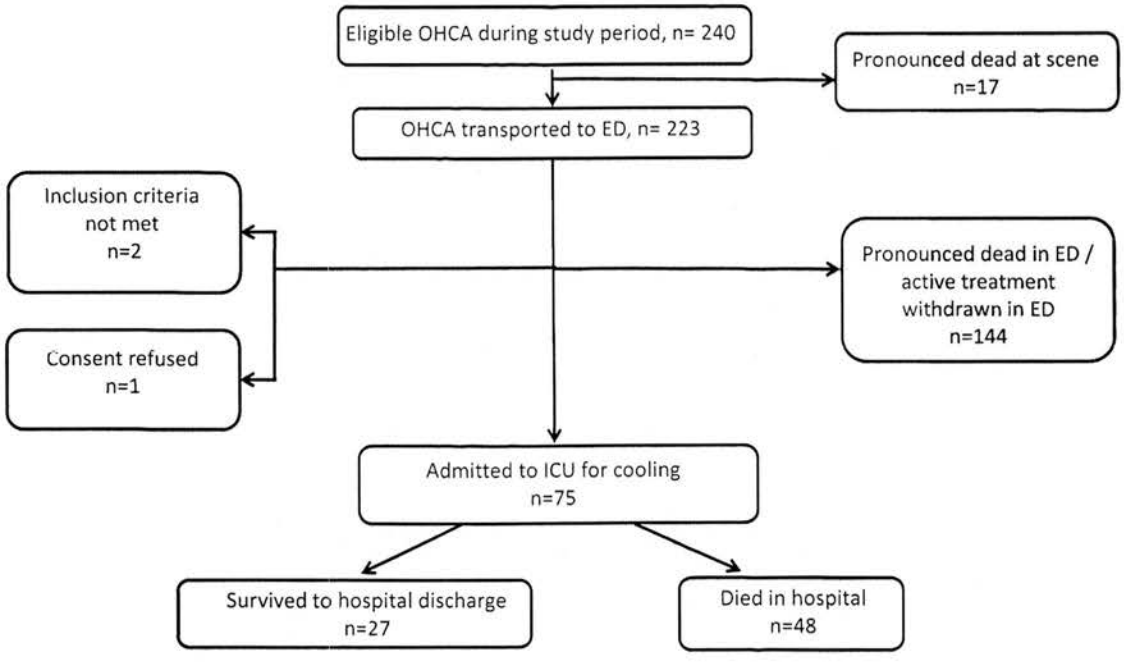
5.1 Total Study Patients

A total of 240 patients were recruited to the TOPCAT study.

5.2 Excluded Study Patients

Three patients were excluded from the study after being recruited. One patient refused consent on re-gaining consciousness in ICU. Two patients regained consciousness in the ED, were extubated and subsequently withdrawn from the study. A total of 237 patients were included in the final analysis. A summary of patient recruitment is shown in Figure 5.1.

Figure 5.1. Patient recruitment to the TOPCAT study



5.3 General demographics of recruited patients

A descriptive analysis of baseline characteristics of the patients recruited to the TOPCAT study is shown in Table 5.1

Table 5.1 Patients recruited to the TOPCAT study

Demographics	All patients (n=237)
Age in years, mean ± SD	65.3 ± 17
Male sex, n (%)	153 (65)
Details of cardiac arrest	
Cause of cardiac arrest presumed cardiac, n (%)	182 (77)
Bystander witnessed cardiac arrest, n(%)	104 (44)
Received bystander CPR, n(%)	115 (49)
First cardiac rhythm VF/VT, n (%)	102 (43)
First cardiac rhythm PEA, n (%)	48 (20)
First cardiac rhythm asystole, n(%)	77 (32)
First cardiac rhythm unknown, n(%)	10 (4%)
Time in minutes from 999 call to arrival of first ambulance crew, median (IQR)	7 (4-10)
Adrenaline (mg) given during resuscitation, mean ± SD	4 ± 3.5
Achieved ROSC, n(%)	104 (44)
Time in minutes from call to ROSC, median (IQR)	25 (17-32)
Time in minutes from ROSC to arrival at the ED, median (IQR)	30 (23-37)
Outcome	
Survived to ICU admission, n(%)	74 (31)
Survived to hospital discharge, n(%)	27 (11)

5.4 Patient outcome

During the study period, 75 patients survived to hospital admission and 27 survived to hospital discharge. Of those who survived to hospital discharge, the majority had a favourable neurological outcome, achieving a CPC score of 1 or 2 within 6-months following discharge, as shown in Table 5.2.

Table 5.2 Best cerebral performance category (CPC) achieved within 6-months of patients surviving to hospital discharge.

Best CPC score within 6-months post OHCA	Survivors to hospital discharge (n=27)
CPC 1, n (%)	15 (56)
CPC 2, n (%)	5 (19)
CPC 3, n (%)	5 (19)
CPC 4, n (%)	0
Dead at 6 months	2 (7)

Of the patients who achieved ROSC but died in ICU (n=49), the primary cause of death was severe neurological injury in 28 (57%) patients, multi-organ failure in 14 (29%) isolated cardiovascular failure in 5 (10%) and sudden in-hospital cardiac arrest in 2 (4%).

5.5 Exclusions from core body temperature analysis

One patient suffered a suspected OHCA from hypothermia (Core temperature 23°C). Research blood samples were not taken by the attending ED doctor. This patient was removed from subsequent analysis and died 20 hours after admission.

The cause of OHCA was overwhelming sepsis in one patient who presented to the ED in cardiac arrest with a core body temperature of 39.5°C. No research blood samples were taken by the attending ED doctor. This patient was not included in subsequent temperature analysis.

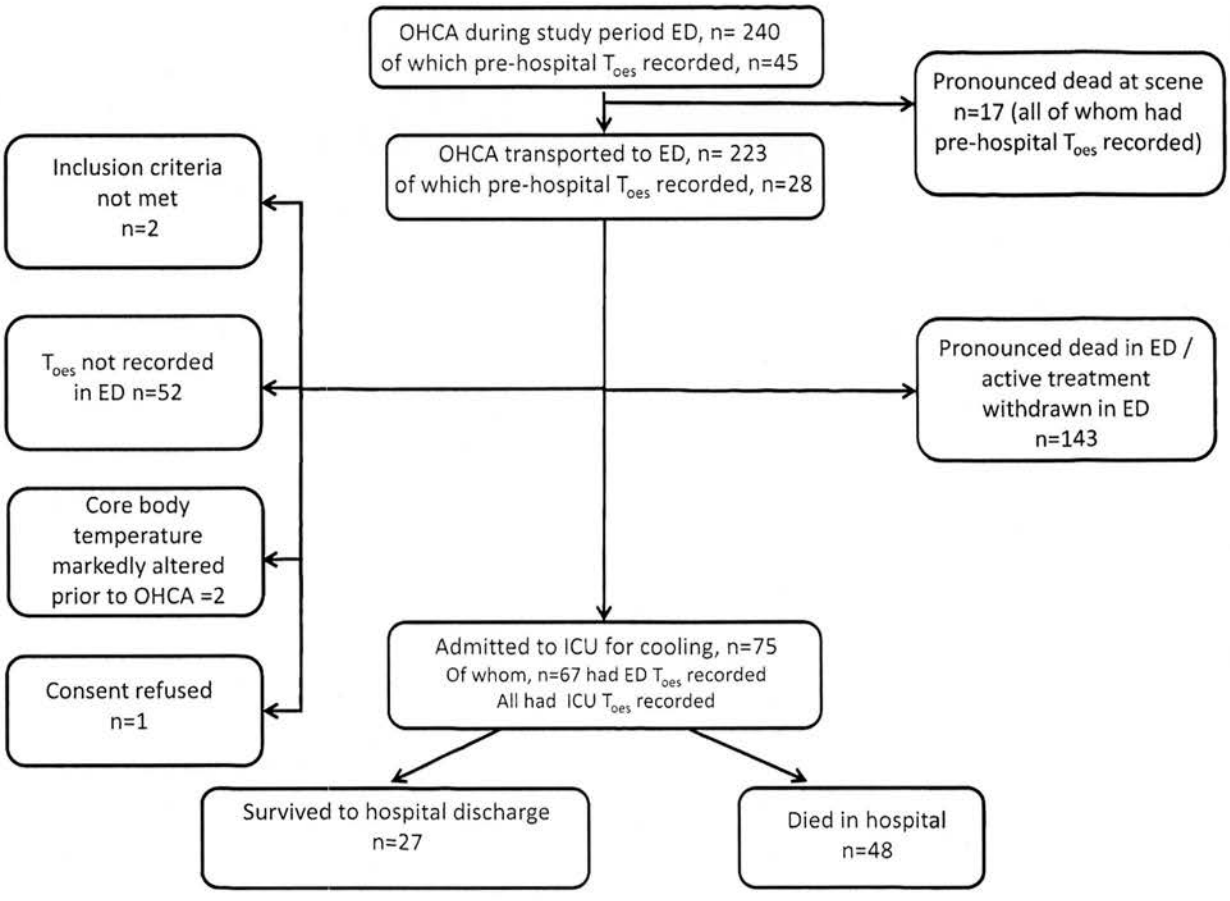
5.6 Complications of oesophageal temperature monitoring

On arrival in the ED, one patient was noted to have the temperature probe situated next to the cuff of the endotracheal tube on direct laryngoscopy and the probe was re-sited. Otherwise no complications from temperature monitoring were observed.

5.7 Summary of core body temperature analysis

A summary of patient recruitment in relation to oesophageal temperature measurement is shown in Figure 5.2

Figure 5.2 Summary of oesophageal temperature measurements in TOPCAT patients



5.8 Pre-hospital oesophageal temperature

A total of 45 patients had oesophageal temperature monitoring pre-hospital. The mean initial oesophageal temperature on arrival at scene was 33.7°C (95% CI 32.8-34.5).

Patients who achieved ROSC showed a trend towards higher mean pre-hospital oesophageal temperature compared with patients who failed to achieve ROSC (34.4 vs. 33.4, p=0.15).

5.9 Emergency Department oesophageal temperature

A total of 171 patients had oesophageal temperature measured on arrival to the ED. Mean T_{oes} was 34.3°C (95% CI 34.1-34.5) for all patients. Patients who had achieved ROSC and arrived in the ED with a sustained cardiac output had a mean T_{oes} of 34.6°C (95% CI 34.3-34.8).

5.10 Intensive Care Unit oesophageal temperature

Patients surviving to reach admission to ICU had a mean T_{oes} of 34.9 (95% CI 34.6-35.2) on ICU arrival, before cooling was initiated. Patients who survived to reach hospital discharge had a higher T_{oes} on admission to the ICU than patients who subsequently died on ICU (35.6 vs. 34.4, p=0.0006). This is shown in Figure 5.3 and Table 5.3.

Figure 5.3. Mean T_{oes} of post-ROSC out-of-hospital cardiac arrest patients who survived to hospital discharge [▲] (n=27) vs. patients who were admitted to ICU but died in hospital [●] (n=48)

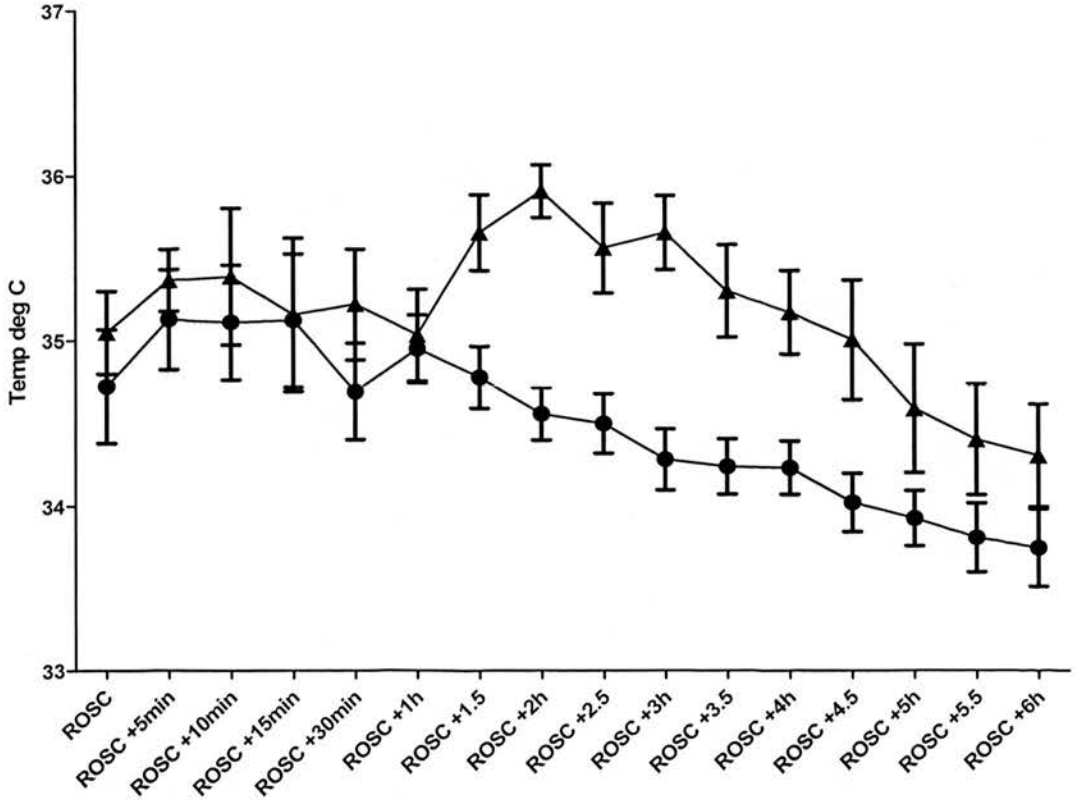


Table 5.3. Core body temperature post-OHCA in patients who survived to discharge compared to patients who died in ICU. sd= standard deviation

	Died ICU		Survived to discharge				
	n	mean (sd)	n	mean (sd)	Difference in means	95% CI for difference	p-value
Core temp pre hospital	8	34.80 (1.36)	7	34.05 (2.37)	-0.75	(-1.54, 3.05)	0.478
Core temp in ED	42	34.53 (1.34)	24	34.97 (1.34)	+0.45	(-1.34, 0.25)	0.201
Core temp in ICU	38	34.42 (1.20)	25	35.66 (1.33)	+1.24	(-1.90, -0.57)	0.001

Patients who survived to hospital discharge appeared to rewarm at a greater rate (mean +0.7° between ED and ICU) compared to patients who died in ICU (mean: no change between ED and ICU), as shown in Table 5.3 and Figures 5.4 and Figure 5.5.

Figure 5.4. Emergency Department and Intensive Care Unit admission oesophageal temperature of post-OHCA patients who survived to hospital discharge (n=27).

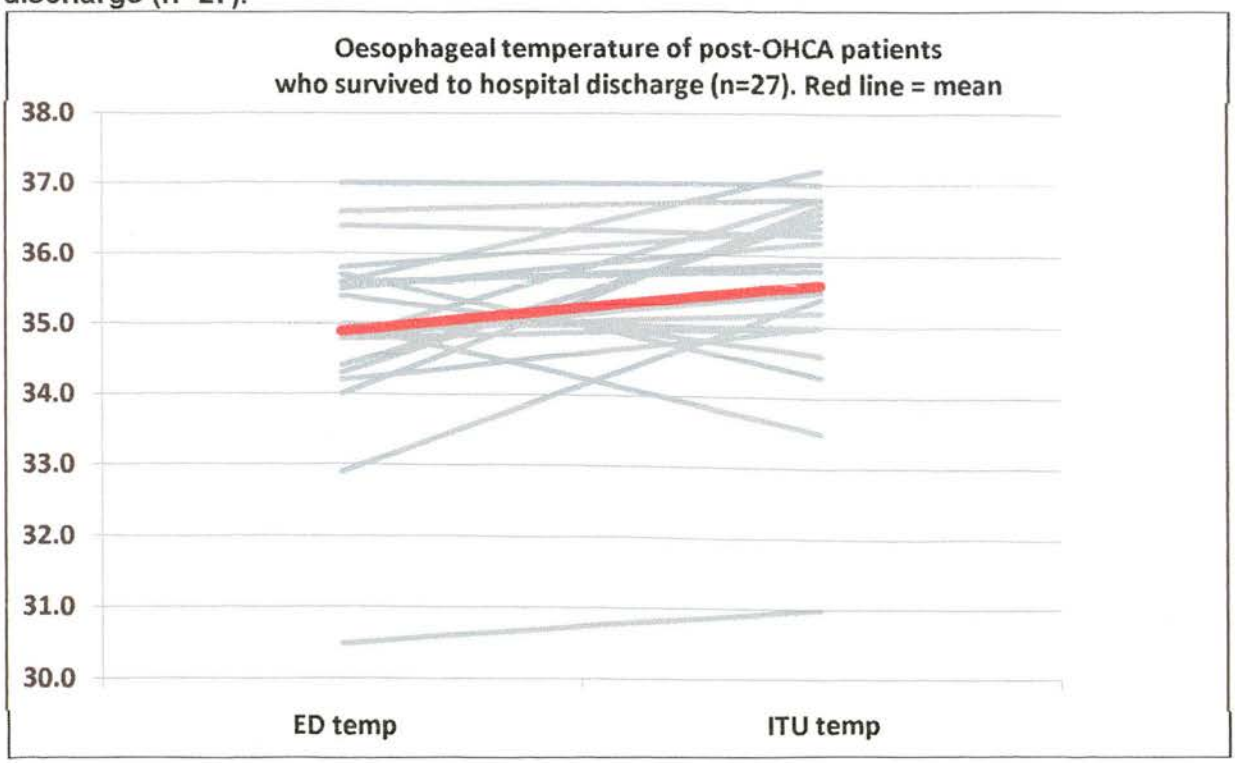
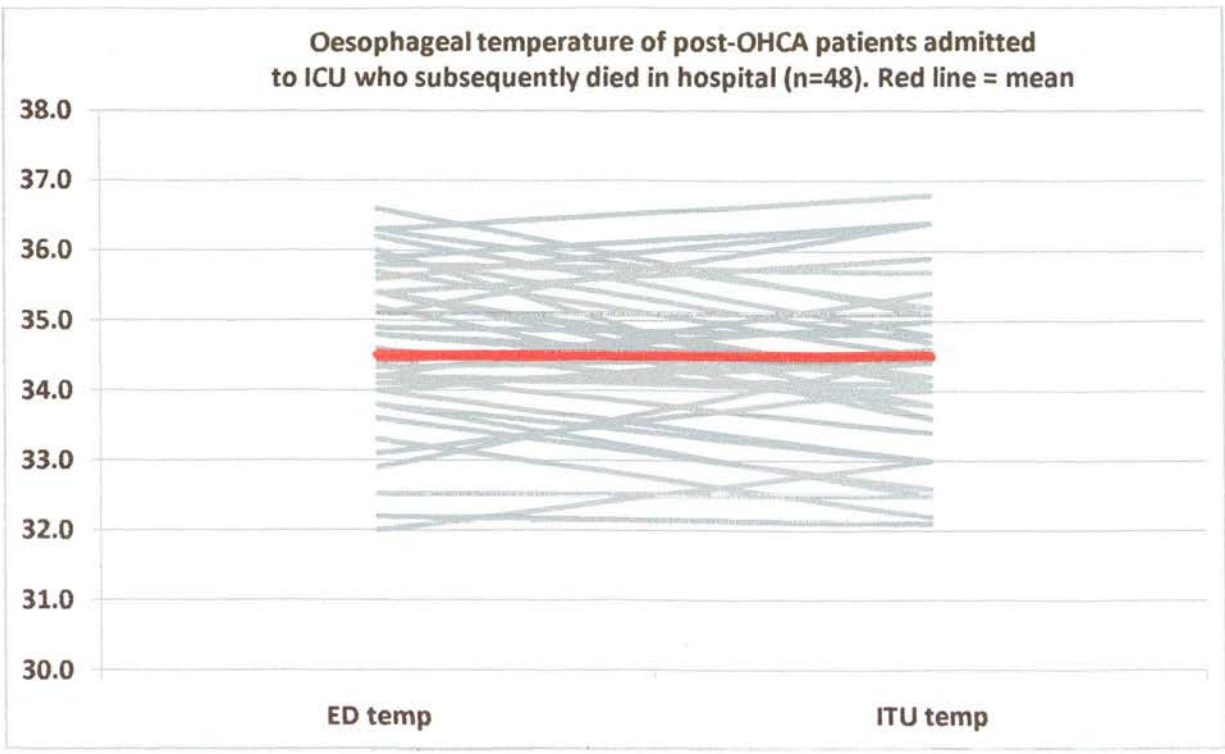


Figure 5.5. Emergency Department and Intensive Care Unit admission oesophageal temperature of post-OHCA patients admitted to ICU who subsequently died in hospital (n=48)



5.11 Survivors of OHCA versus patients who died in the ICU

There were several significant differences between patients who died in ICU and patients who survived to hospital discharge, as shown in Table 5.4. When compared to patients who died in ICU, patients who survived to hospital discharge had a higher incidence of VF/VT as the presenting cardiac rhythm (48 vs. 85%, p=0.002); higher incidence of arrest of presumed cardiac cause (67 vs. 96%, p=0.003) and shorter downtime (29 vs. 11 minutes, p=0.0004). There was no significant difference between survivors and non-survivors in time to ED arrival (27 vs. 30 minutes, p=0.67) and time to ICU admission (140 vs. 173 minutes, p=0.96). All patients admitted to ICU were cooled, however, survivors to hospital discharge took longer to reach target therapeutic temperature (<34°C) than non-survivors (313 vs. 222 mins, p=0.028), as shown in Table 5.4.

Table 5.4. Differences between post-ROSC out-of-hospital cardiac arrest patients who survived to hospital discharge (n=27) and those who died in the Intensive Care Unit (n=48).

Demographics	Died in ICU (n= 48)	Survived to hospital discharge (n=27)	P value
Age in years, mean ± SD	*61 ± 18.7*	*60 ± 12.3*	*p=0.71*
Male sex, n (%)	29 (60)	19 (70)	p=0.45
Details of cardiac arrest			
Cause of cardiac arrest presumed cardiac, n (%)	32 (67)	26 (96)	*p=0.003**
Bystander witnessed cardiac arrest, n(%)	28 (58)	19 (70)	p=0.33
Received bystander CPR, n (%)	24 (50)	17 (63)	p=0.34
First cardiac rhythm VF/VT, n (%)	23 (48)	23 (85)	*p=0.002**
First cardiac rhythm PEA, n (%)	5 (10)	1 (4)	p=0.66
First cardiac rhythm asystole, n(%)	20 (42)	1 (4)	*p=0003**
Time in minutes to arrival of first ambulance crew, *median (IQR)*	*8 (4-12)*	*7 (5-9)*	*p=0.14*
Time in minutes from call to ROSC, median (IQR)	29 (11-46)	11 (5-17)	*p=0.0004**
Time in minutes from ROSC to arrival in ED, median (IQR)	30 (22-38)	27 (22-32)	p=0.67
Transferred from ED for immediate PCI, n(%)	7 (15)	5 (19)	p=0.74
Transferred from ED for radiological imaging prior to ICU admission, n(%)	11 (23)	8 (30)	p=0.58
Transferred from ED direct to ICU, n(%)	30 (63)	14 (52)	p=0.47
Temperature data and cooling data			
Oesophageal temperature on arrival in ED, mean (SD)	34.5 (1.3)	35.0 (1.3)	p=0.20
Oesophageal temperature on arrival in ICU, mean (SD)	34.5 (1.2)	35.6 (1.3)	*p=0.0003**
Time in minutes from ROSC to ICU commencement of cooling, median (IQR)	173 (130-216)	140 (88-192)	p=0.96
Time in minutes from ROSC to target therapeutic temperature, median (IQR)	222 (141-303)	313 (220-406)	*p=0.028**

5.12 Early in-hospital physiology following OHCA

Aside from the significant difference in T_{oes} on arrival in the ICU between survivors and non-survivors several other physiological differences were observed, as shown in Table 5.5. On admission to ICU, serum hydrogen concentration was significantly lower in survivors compare to non-survivors (47.4 vs. 78.4 nmol/L, p=0.001) and serum lactate concentration was lower in survivors (1.6 vs. 5.3 mmol/L, p=0.003). Less adrenaline was given as a resuscitation drug during the pre-hospital and ED phases of care in survivors compared to non-survivors (1.4mg vs. 3.1mg, p=0.04)

Table 5.5 Early in-hospital cardiovascular physiology of survivors and non-survivors of OHCA

Emergency Department	Died in ICU (n= 48)	Survived to hospital discharge (n=27)	P value
Mean arterial pressure, mean ± SD	83 (25)	88 (17.7)	p=0.47
Serum hydrogen concentration (nmol/L), mean± SD	98.1 (38)	84.0 (39.7)	p=0.15
Serum lactate (mmol/L), mean± SD	10.1 (3.7)	8.5 (4.4)	p=0.11
Total adrenaline (mg) used during initial resuscitation, mean ± SD	3.1 (3.1)	1.4 (3.4)	*p=0.04*
Intensive Care Unit			
Mean arterial pressure, mean ± SD	85 (17)	90 (14)	p=0.90
Number of patients requiring intropic support at ICU admission (%)	20 (42%)	6 (22%)	p=0.15
Serum hydrogen concentration (nmol/L), mean± SD	78.4 (32.3)	47.4 (6.1)	*p=0.001*
Serum lactate (mmol/L), mean± SD	5.3 (3.9)	1.6 (0.7)	*p=0.003*

5.13 Summary – oesophageal temperature post OHCA

Following OHCA in Edinburgh, all patients have oesophageal temperatures below normothermia in the pre-hospital phase and on arrival in the Emergency Department. Patients who achieve ROSC following OHCA and survive to hospital discharge are warmer on arrival in ICU and take longer to reach target MTH temperatures compared to patients who die in hospital.

Chapter 6

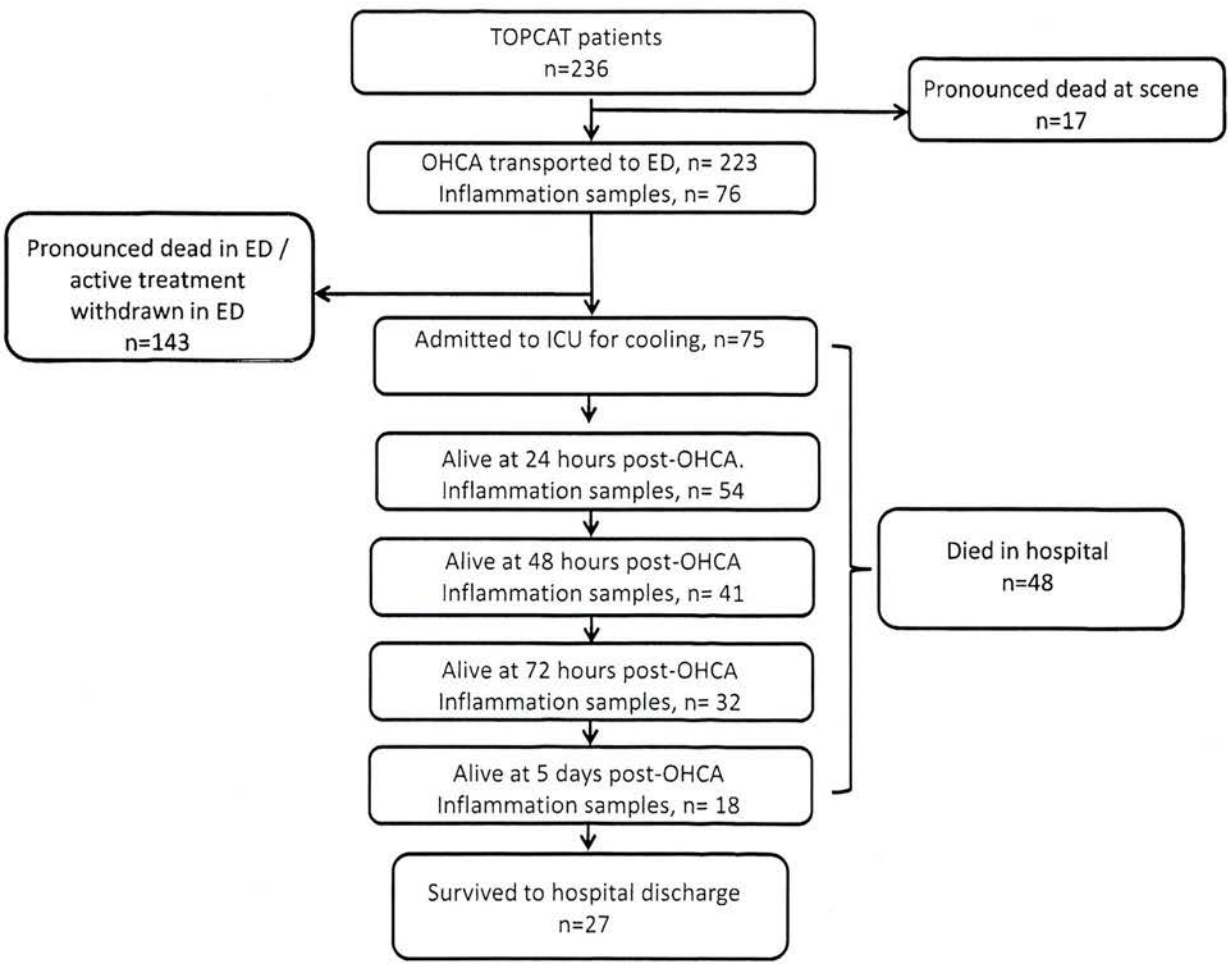
Results – Systemic Inflammation & neutrophil activity post-OHCA

6.1 Markers of systemic inflammation data

Blood samples were taken and analysed for serum inflammatory markers on a total of 14 patients pre-hospital, 76 patients in the ED, 54 patients at 24-hours post-OHCA, 41 patients at 48-hours post-OHCA, 32 patients at 72-hours post-OHCA and 18 patients 5-days post-OHCA.

The overall collection of blood samples for serum inflammatory marker analysis is shown in Figure 6.1.

Figure 6.1. TOPCAT serum samples collected for inflammatory marker analysis



6.2 Incomplete data

13 patients who survived to hospital discharge did not have a complete set of blood samples for serum inflammatory marker assay. This was predominantly from the day-5 sample not being taken. 21 of the 27 patients who survived to hospital discharge had a complete set of blood samples apart from the day-5 time point.

Five samples showed an error during laboratory assay and were excluded from subsequent analysis.

Due to limited assay kit availability, 50 patients who had blood samples taken in the ED but had never achieved ROSC did not have these samples assayed. The objective was to look for any pattern in markers of inflammation post-OHCA and we felt analysis of 93 patients who never achieved ROSC would be sufficient in pilot form.

6.3 Interleukin-1β

Interleukin-1β did not appear to be significantly raised in post-OHCA patients as compared to healthy volunteers. The progression of interleukin-1β for all patients post-OHCA is shown in Figure 6.2. There did not appear to be any significant difference in IL-1β levels between survivors and non-survivors in patients who achieved ROSC, as shown in Figure 6.3.

Figure 6.2 Interleukin-1β post-OHCA – all patients

PH= pre-hospital; ED= Emergency Department; 24=24 hours post-OHCA; 5D= 5 days post-OHCA; HV= healthy volunteers. Horizontal line depicts sample mean.

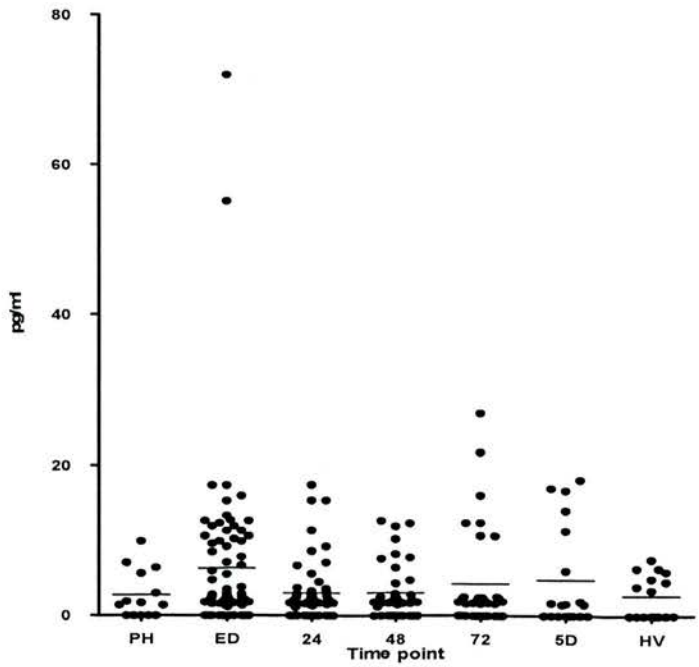
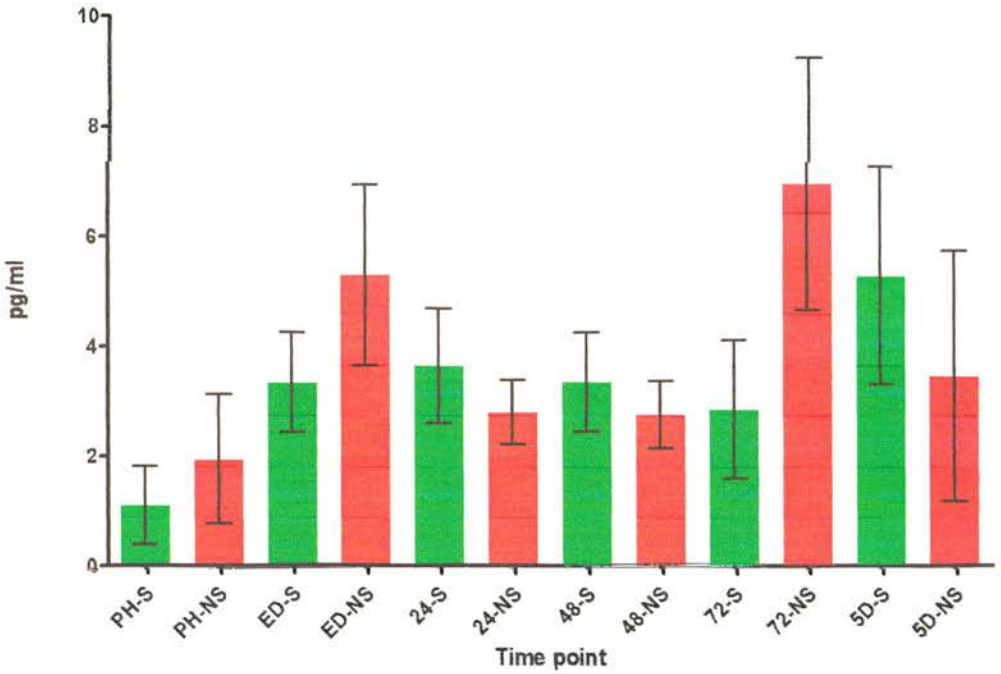


Figure 6.3 Interleukin-1β post-OHCA in patients who achieved ROSC
PH= pre-hospital; ED= Emergency Department; 24=24 hours post-OHCA; 5D= 5 days post-OHCA; Error bars=standard error of the mean



6.4 Interleukin-6

IL-6 was not significantly raised in the pre-hospital phase following OHCA but rose from ED admission and peaked at 48 hours following ROSC. The progression IL-6 for all patients post-OHCA is shown in Figure 6.4. Non-survivors showed a non-significant trend towards higher IL-6 levels at all time points, as shown in Figure 6.5. The area under the ROC curve for IL-6 to predict in-hospital death for patients who achieved ROSC was 0.757 (95% CI 0.59-0.92).

Figure 6.4 IL-6 post-OHCA

PH= pre-hospital; ED= Emergency Department; 24=24 hours post-OHCA; 5D= 5 days post-OHCA; HV= healthy volunteers. Horizontal line depicts sample mean.

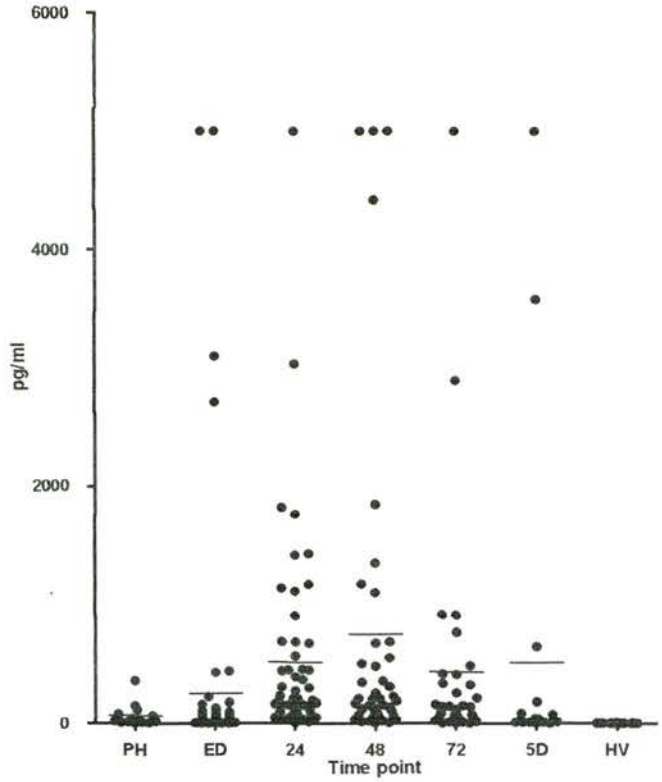
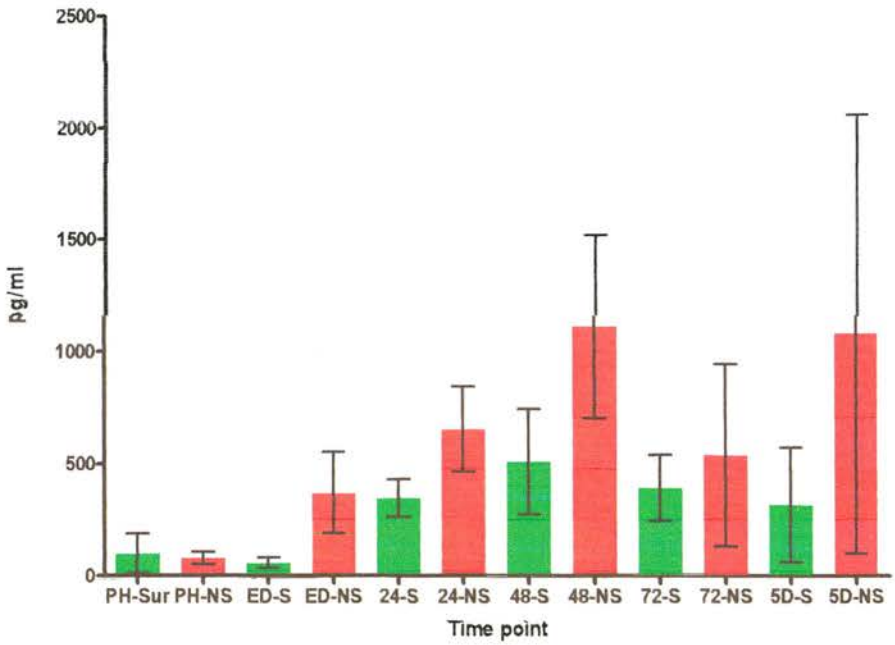


Figure 6.5. IL-6 in patients who achieved ROSC following OHCA

Green/S=survived to hospital discharge; Red/NS=non-survivor, died in ICU; PH=pre-hospital; ED=Emergency Department; 24=24-hours post-ROSC; 5D=5-days post-ROSC. Error bars= standard error of the mean.



6.5 Interleukin-8

IL-8 appeared to be significantly raised in patients following OHCA. Increased serum IL-8 was detectable in the pre-hospital and ED phases, with IL-8 reaching peak levels at 24-hours post-ROSC. The progression of IL-8 for all patients post-OHCA is shown in Figure 6.6. IL-8 levels were significantly higher in non-survivors on arrival at 24-hours (627.2 vs 196.7pg/ml, p=0.02) and 48-hours (555.1 vs 151.1 p=0.05) post-ROSC. There was a trend towards high levels of IL-8 measured in the ED in non-survivors compared to survivors (347.1 vs 86.0 pg/ml, p=0.17). IL-8 appeared to return to normal baseline levels at 5 days in survivors but remained significantly elevated in non-survivors at 5-days (625.1 vs 66.8 pg/ml, p=0.04), as shown in Figure 6.7.

2 patients showed significantly higher levels of IL-8, accounting for the 5 highest points in Figure 6.6. The first patient had an OHCA of primary cardiac origin and the second patient suffered a respiratory arrest from chronic obstructive pulmonary disease, without preceding infective symptoms. There were no major differences between these patients and the rest of the study cohort.

Figure 6.6 Interleukin-8 post-OHCA
PH= pre-hospital; ED= Emergency Department; 24=24 hours post-OHCA; 5D= 5 days post-OHCA; HV= healthy volunteers. Horizontal line depicts sample mean.

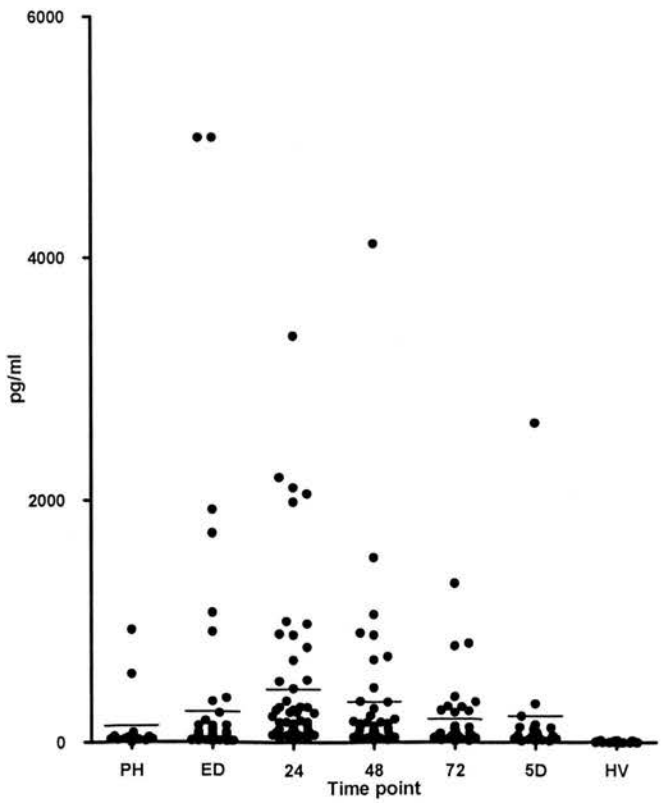
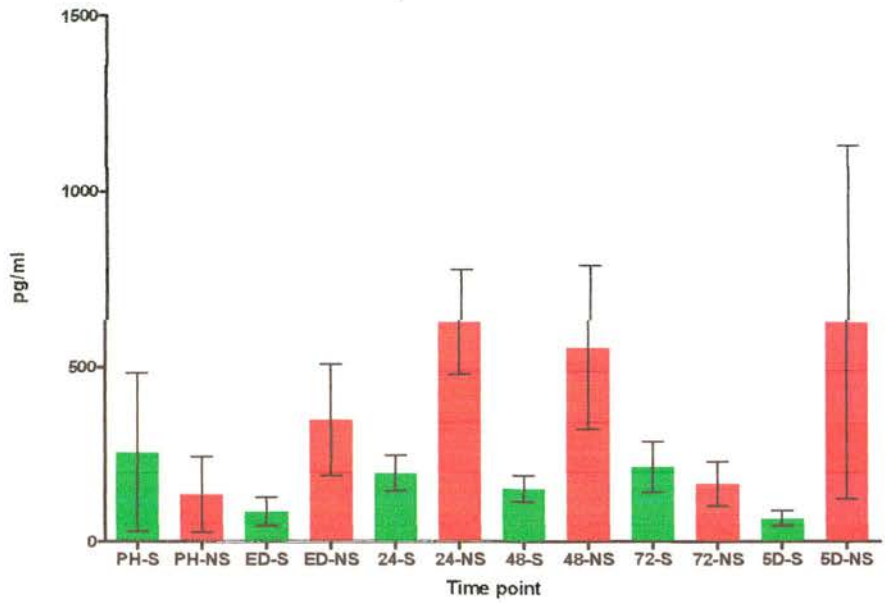


Figure 6.7. Interleukin-8 in patients who achieved ROSC following OHCA
Green/S=survived to hospital discharge; Red/NS=non-survivor, died in ICU; PH=pre-hospital; ED=Emergency Department; 24=24-hours post-ROSC; 5D=5-days post-ROSC. Error bars= standard error of the mean.



6.6 Interleukin-10

IL-10 was significantly raised in all patients post-OHCA and remained consistently elevated in the 5-days following ROSC. The progression of IL-10 for all patients post-OHCA is shown in Figure 6.8. At the ED time point, no significant difference was observed in the levels of IL-10 in survivors and non-survivors (27.8 vs 32.1 pg/ml, p=0.84). Non-survivors had higher levels of IL-10 at 24-hours (70.5 vs 14.2 pg/ml, p=0.01) and 48-hours (63.1 vs 22.2 pg/ml, p=0.05) post-ROSC with a trend towards higher levels at 72-hours and 5-days post-ROSC, as shown in Figure 6.9.

Figure 6.8 Interleukin-10 post-OHCA

PH= pre-hospital; ED= Emergency Department; 24=24 hours post-OHCA; 5D= 5 days post-OHCA; HV= healthy volunteers. Horizontal line depicts sample mean.

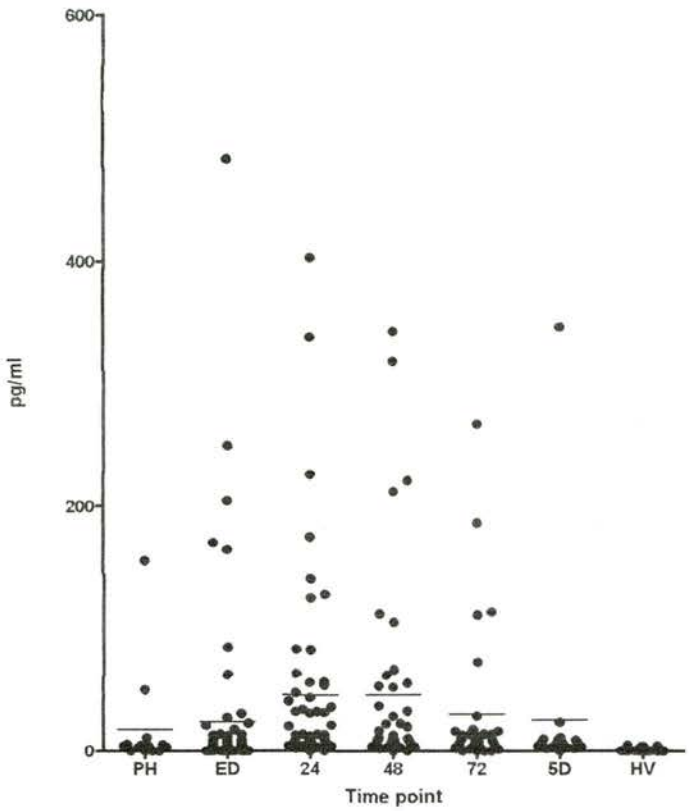
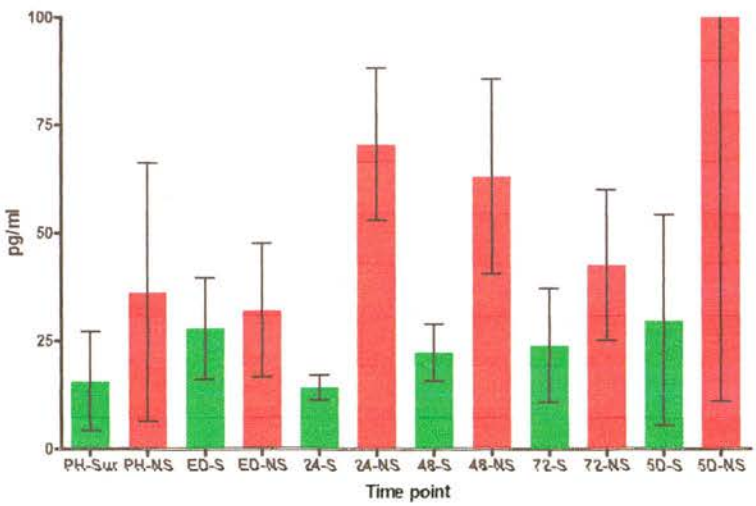


Figure 6.9. IL-10 in patients who achieved ROSC following OHCA

Green/S=survived to hospital discharge; Red/NS=non-survivor, died in ICU; PH=pre-hospital; ED=Emergency Department; 24=24-hours post-ROSC; 5D=5-days post-ROSC. Error bars= standard error of the mean.



6.7 Interleukin-12

IL-12 levels were mildly elevated from baseline in patients following OHCA, with a peak at 72-hours post-ROSC. The progression of interleukin-10 for all patients post-OHCA is shown in Figure 6.10. No significant differences in IL-12 level were observed between survivors and non-survivors, as shown in Figure 6.11.

One patient, who suffered a respiratory and subsequent cardiac arrest following an asthma attack, accounted for the 3 highest IL-12 values, measured in the ED and at 24- and 48-hours post-ROSC.

Figure 6.10 IL-12 post-OHCA
PH= pre-hospital; ED= Emergency Department; 24=24 hours post-OHCA; 5D= 5 days post-OHCA; HV= healthy volunteers. Horizontal line depicts sample mean.

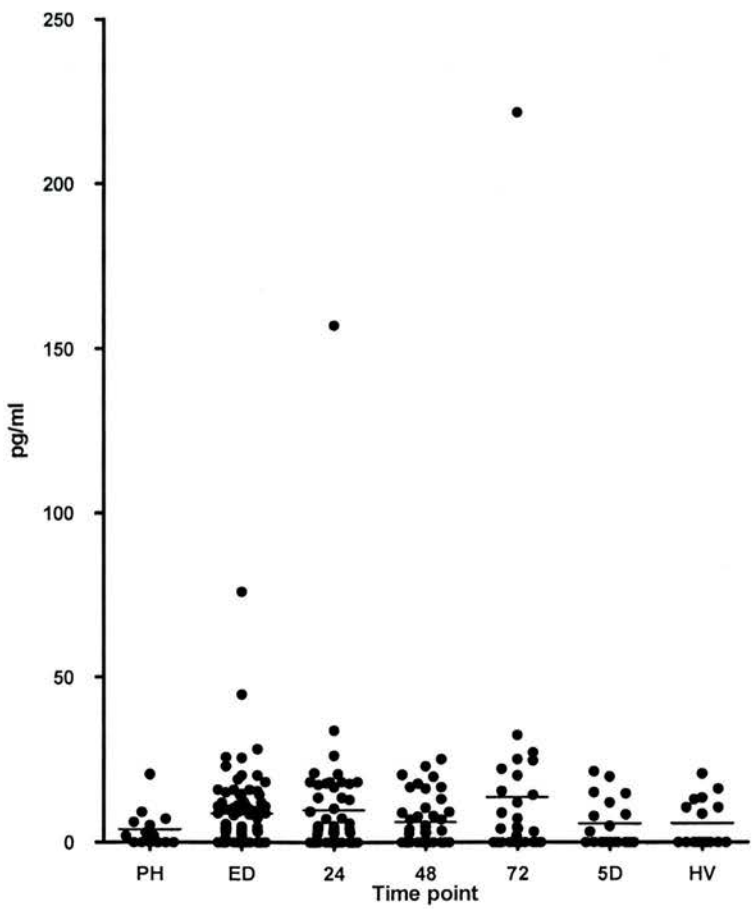
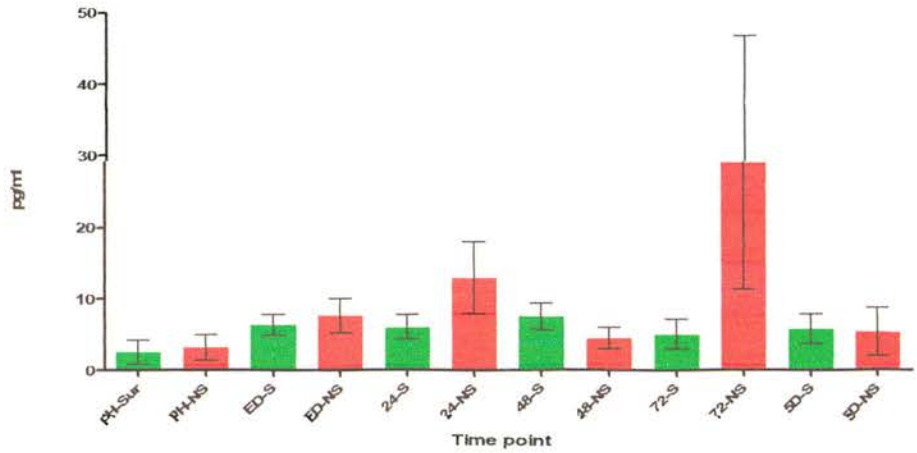


Figure 6.11. Interleukin-12 in patients who achieved ROSC following OHCA
Green/S=survived to hospital discharge; Red/NS=non-survivor, died in ICU; PH=pre-hospital; ED=Emergency Department; 24=24-hours post-ROSC; 5D=5-days post-ROSC. Error bars= standard error of the mean. When the single patient with disproportionately high IL-12 at 72-hours was removed from analysis, no significant difference was observed between survivors and non-survivors.



6.8 Tumour necrosis factor-alpha

Serum levels of TNF-α were mildly raised from ED admission in patients following OHCA, although levels were not significantly higher than healthy volunteers. The progression of TNF-α for all patients post-OHCA is shown in Figure 6.12. There did not appear to be any significant differences in levels of TNF-α between survivors and non-survivors, as shown in Figure 6.13.

Figure 6.12 TNF-α post-OHCA

PH= pre-hospital; ED= Emergency Department; 24=24 hours post-OHCA; 5D= 5 days post-OHCA; HV= healthy volunteers. Horizontal line depicts sample mean.

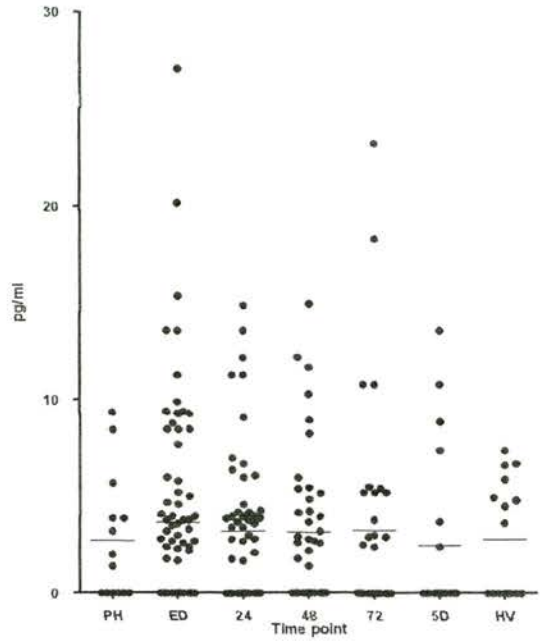
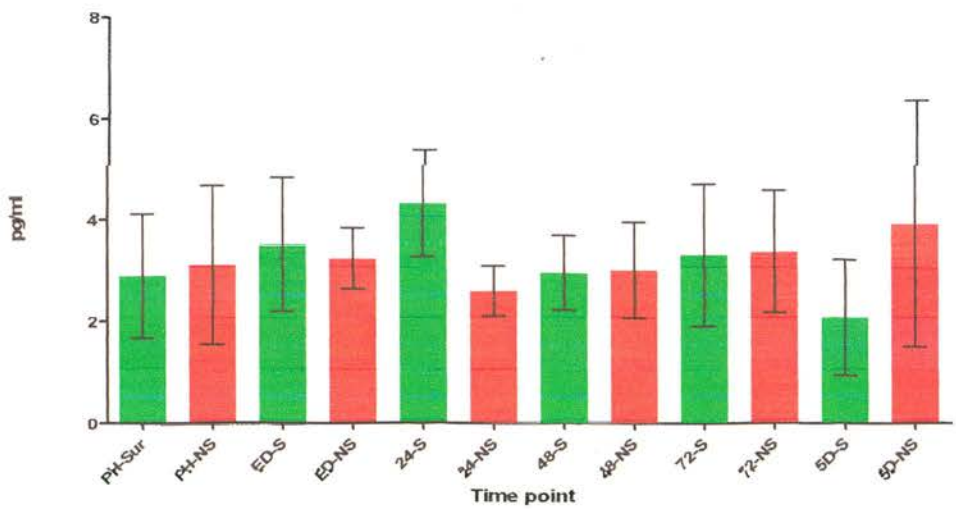


Figure 6.13. TNF-α in patients who achieved ROSC following OHCA

Green/S=survived to hospital discharge; Red/NS=non-survivor, died in ICU; PH=pre-hospital; ED=Emergency Department; 24=24-hours post-ROSC; 5D=5-days post-ROSC. Error bars= standard error of the mean.



6.9 Markers of neutrophil activation

7 patients, all of whom achieved ROSC, had blood samples taken and processed immediately for cell surface markers on polymorphonuclear leucocytes, indicating neutrophil activation,

including 4 patients with pre-hospital blood sampling. The results of neutrophil activation markers are shown in Figures 6.14-6.17.

Figure 6.14. CD11b neutrophil expression post-OHCA

PH= pre-hospital; ED= Emergency Department; 24h=24 hours post-OHCA; 5D=5 days post-OHCA;HV= healthy volunteers. MCF= mean cell fluorescence. Horizontal line depicts sample mean.

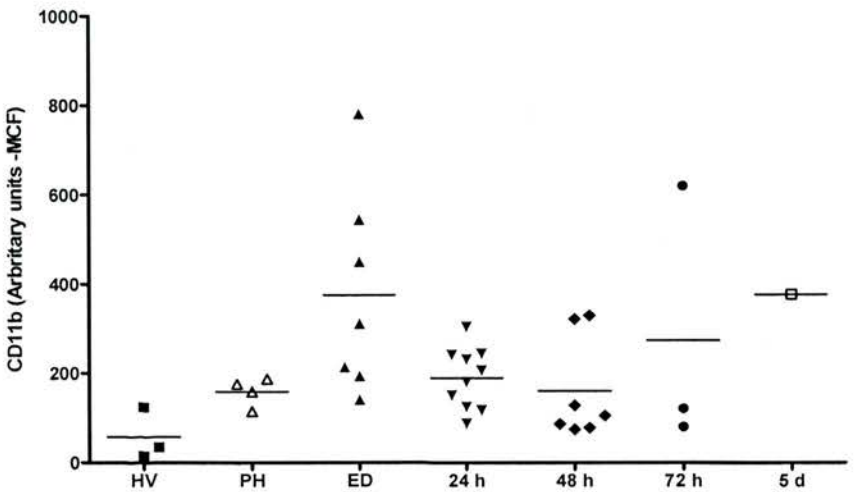


Figure 6.15. CD62L neutrophil expression post-OHCA

PH= pre-hospital; ED= Emergency Department; 24h=24 hours post-OHCA; 5D=5 days post-OHCA;HV= healthy volunteers. MCF= mean cell fluorescence. Horizontal line depicts sample mean.

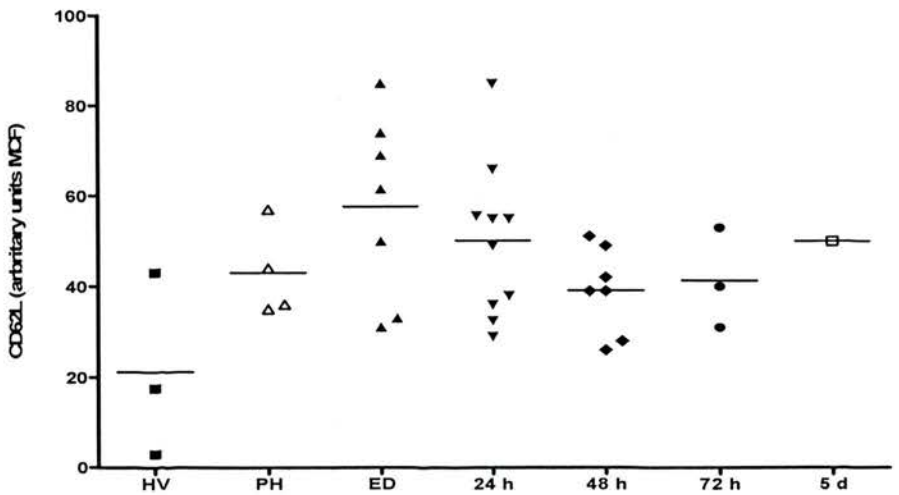


Figure 6.16. CD64 neutrophil expression post-OHCA

PH= pre-hospital; ED= Emergency Department; 24h=24 hours post-OHCA; 5D=5 days post-OHCA;HV= healthy volunteers. MCF= mean cell fluorescence. Horizontal line depicts sample mean.

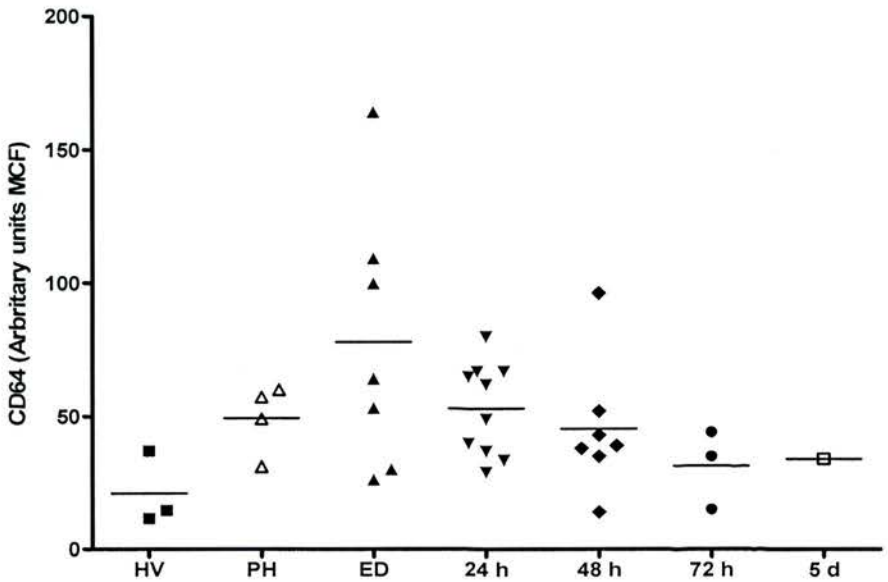
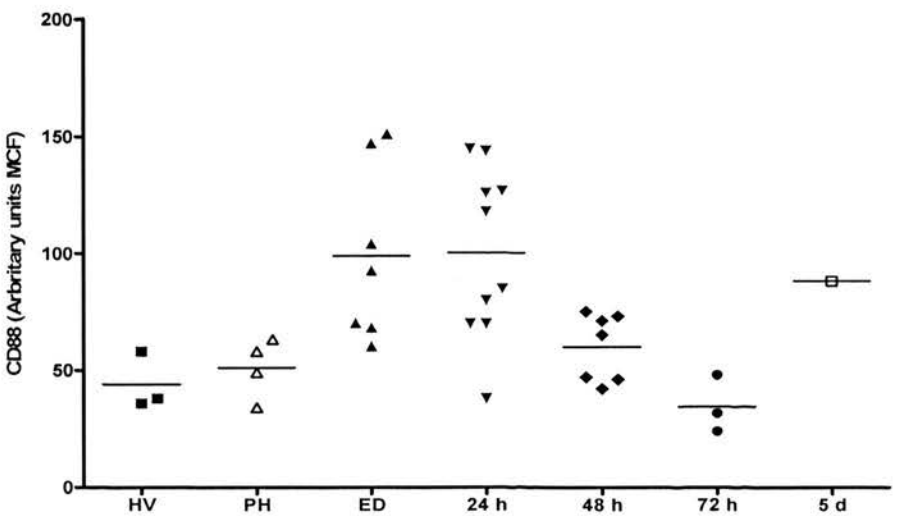


Figure 6.17. CD88 neutrophil expression post-OHCA

PH= pre-hospital; ED= Emergency Department; 24h=24 hours post-OHCA; 5D=5 days post-OHCA; HV= healthy volunteers. MCF= mean cell fluorescence. Horizontal line depicts sample mean.

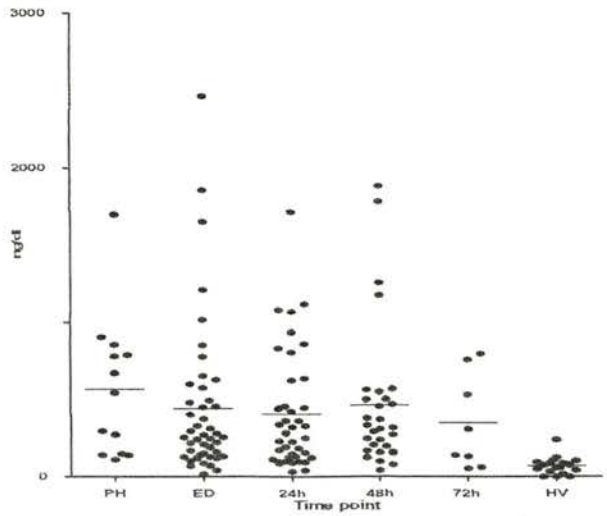


6.10 Human neutrophil elastase

Serum human neutrophil elastase (HNE) was assayed in all patients who had VF as the presenting cardiac rhythm and who achieved ROSC (n=56). When compared to healthy

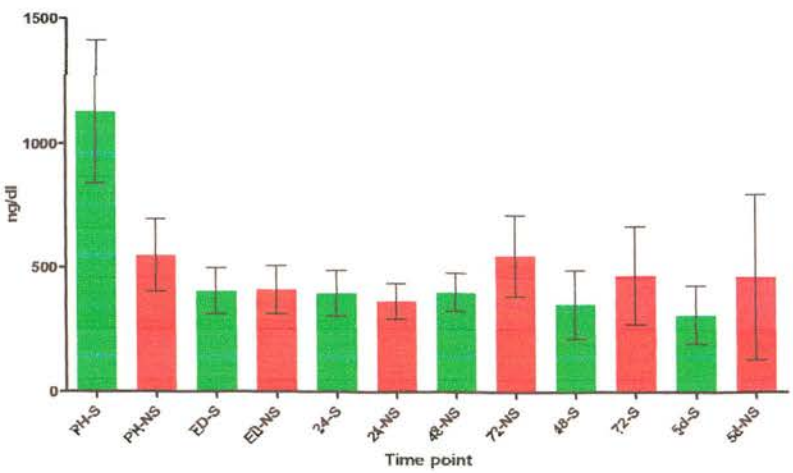
volunteers, HNE was raised in all patients and was detectable during CPR and in the immediate post-ROSC period, remaining elevated in the days following ROSC. This is shown in Figure 6.18.

Figure 6.18. Human neutrophil elastase post-OHCA – all patients
PH= pre-hospital; ED= Emergency Department; 24h=24 hours post-OHCA;HV= healthy volunteers. Horizontal line depicts sample mean.



Overall, there did not appear to be a significant difference in levels of HNE between survivors and non-survivors. A small difference was observed in the pre-hospital samples, with a trend towards higher levels of HNE in the survivors group, although it should be remembered that only a small number of pre-hospital samples were collected for HNE assay (n=13). HNE levels in survivors and non-survivors are shown in Figure 6.19.

Figure 6.19. Human neutrophil elastase in survivors and non-survivors of VF-OHCA
Green/S=survived to hospital discharge; Red/NS=non-survivor, died in ICU; PH=pre-hospital; ED=Emergency Department; 24=24-hours post-ROSC; 5D=5-days post-ROSC. Error bars= standard error of the mean.



6.11 Markers of systemic inflammation and cardiovascular indices

Spearman and Pearson correlations were performed between markers of systemic inflammation and cardiovascular indices. There did not appear to be any significant correlation between markers of systemic inflammation and core body temperature, downtime, serum lactate or serum hydrogen ion concentration.

6.12 Summary of inflammation post-OHCA

Inflammatory cytokinaemia and presence of surface markers of neutrophil activation indicate systemic inflammation is occurring at a very early stage post-OHCA. The inflammatory response persists for several days following OHCA.

Different elements of the inflammatory response occur at different time points following OHCA. Significantly high levels of IL-6 and IL-8 are detectable in the early post-ROSC phase, IL-10 peaks at 24-48 hours post-ROSC and IL-12 peaks at 72-hours post-ROSC. There appear to be significant differences in the levels of IL-6, IL-8, IL-10 and IL-12 between OHCA patients who achieved ROSC and survived to hospital discharge and those who achieved ROSC died in ICU.

Chapter 7

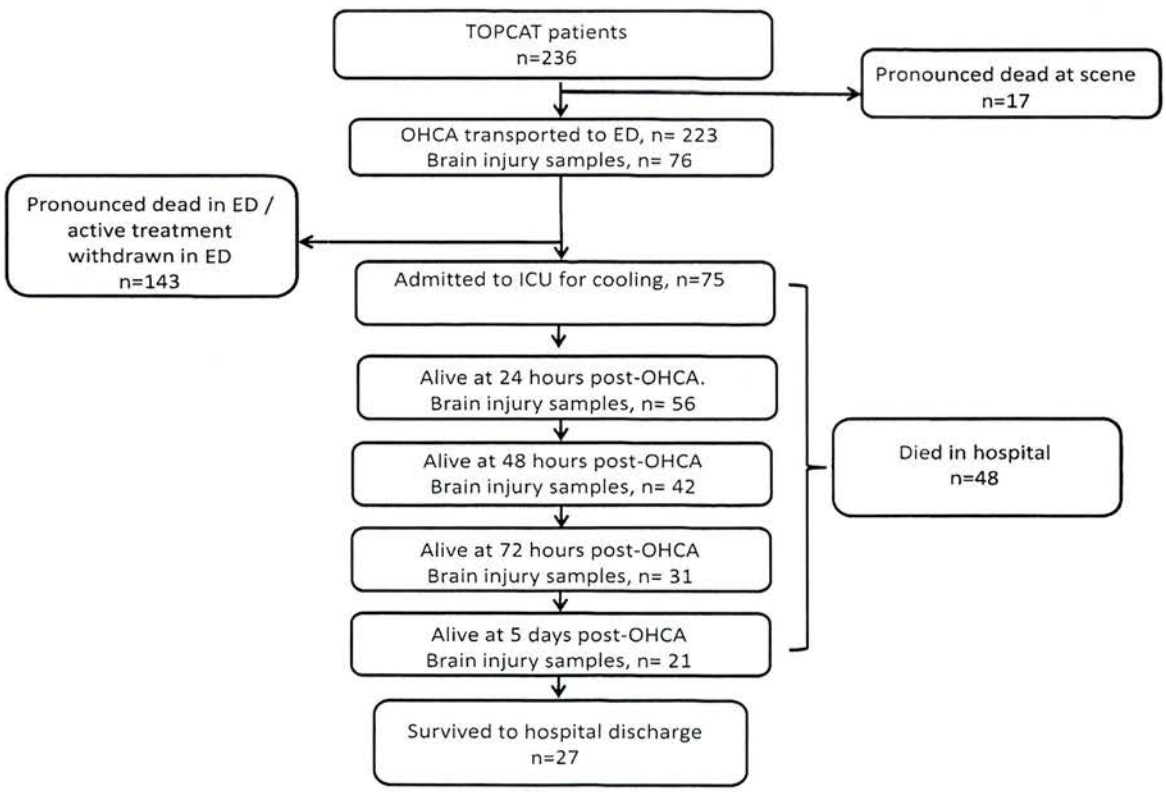
Results – Brain Injury Markers post-OHCA

7.1 Markers of brain injury samples

Blood samples were taken for analysis of brain injury markers (S100b, NSE) on a total of 21 patients pre-hospital, 153 patients in the ED, 56 patients at 24-hours post-OHCA, 42 patients at 48-hours post-OHCA, 31 patients at 72-hours post-OHCA and 21 patients 5-days post-OHCA.

Additional separate funding was obtained to perform a limited number of GFAP assays. GFAP was measured in 38 patients with VF as the initial presenting rhythm who then achieved ROSC. The overall collection of blood samples for NSE and S100b analysis is shown in Figure 7.1.

Figure 7.1 Markers of brain injury samples



7.2 Data collection

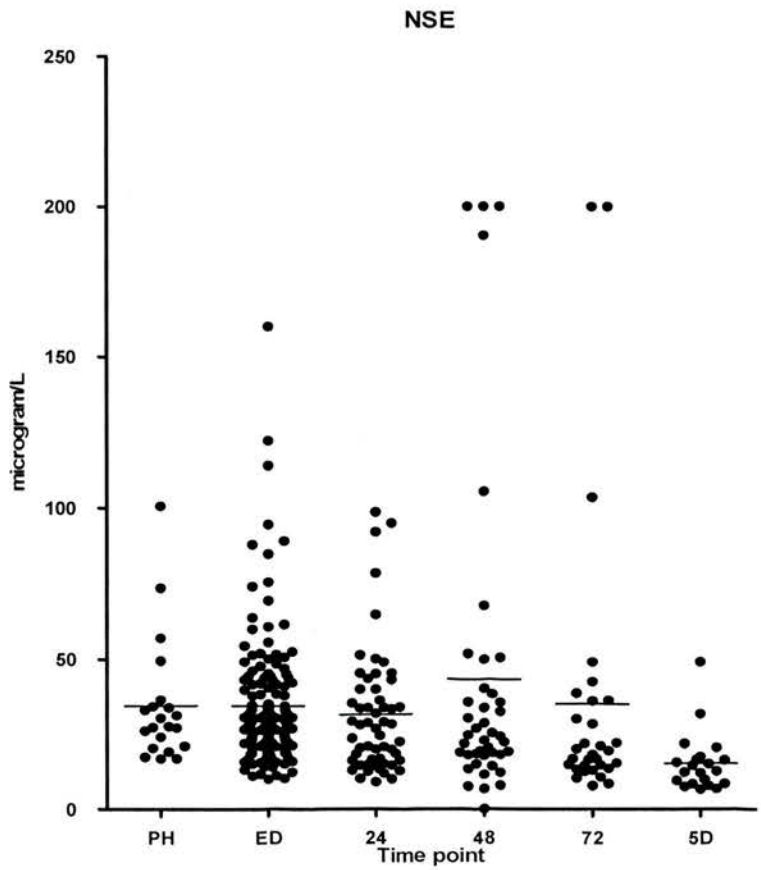
21 of the 27 patients who survived to hospital discharge had a complete set of blood samples apart from the day-5 time point. 13 patients who survived to hospital discharge did not have a complete set of blood samples for serum markers of brain injury assay. This was predominantly from the day-5 sample not being taken.

8 samples did not assay correctly on the automated Liaison analyser and were excluded from subsequent analysis.

7.3 Neuron-specific enolase

NSE was detectable in all patients post-OHCA. Mean serum NSE appeared to reach maximal levels at 48-hours post OHCA. The progression of NSE post-OHCA for all patients is shown in Figure 7.2.

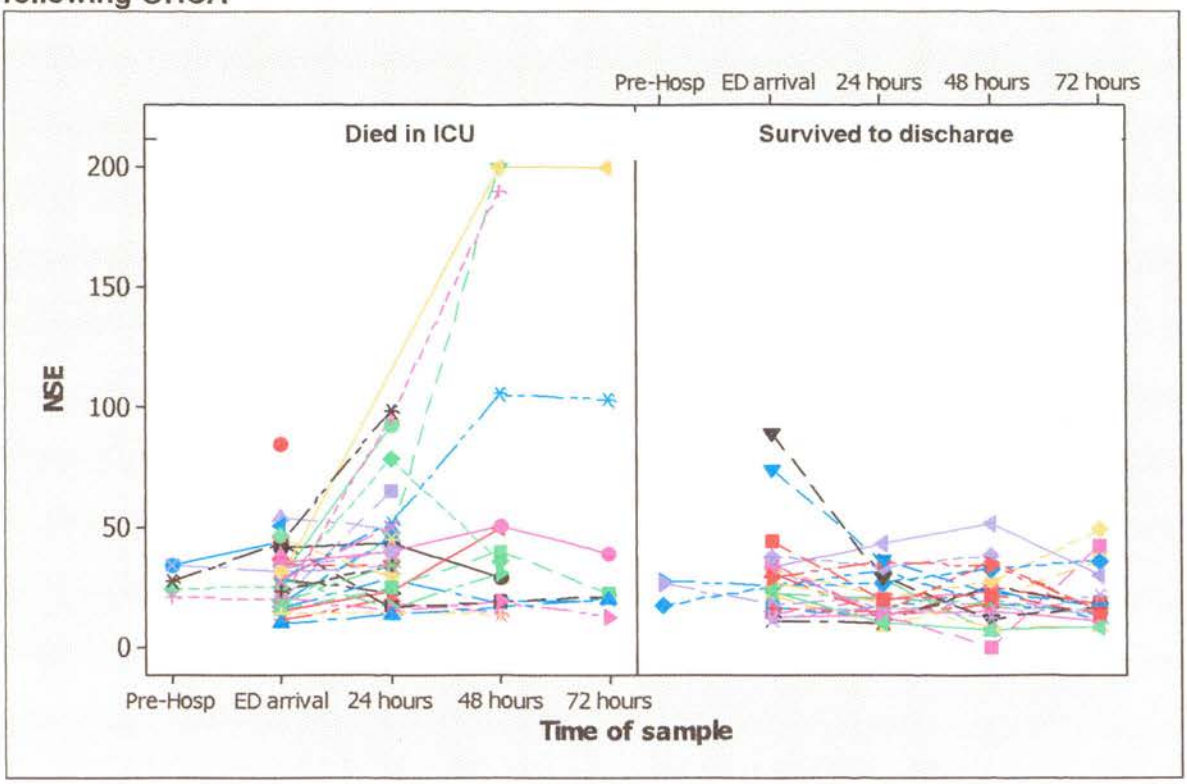
Figure 7.2 Neuron-specific enolase post-OHCA for all patients
PH= pre-hospital; ED= Emergency Department; 24=24 hours post-OHCA; 5D= 5 days post-OHCA; Horizontal line depicts sample mean.



7.4 Neuron-specific enolase post-OHCA in survivors versus non-survivors

Post-OHCA patients who survived to hospital discharge had decreasing levels of NSE over the first 72-hours post-ROSC compared to patients who achieved ROSC but died in ICU, as shown in Figure 7.3

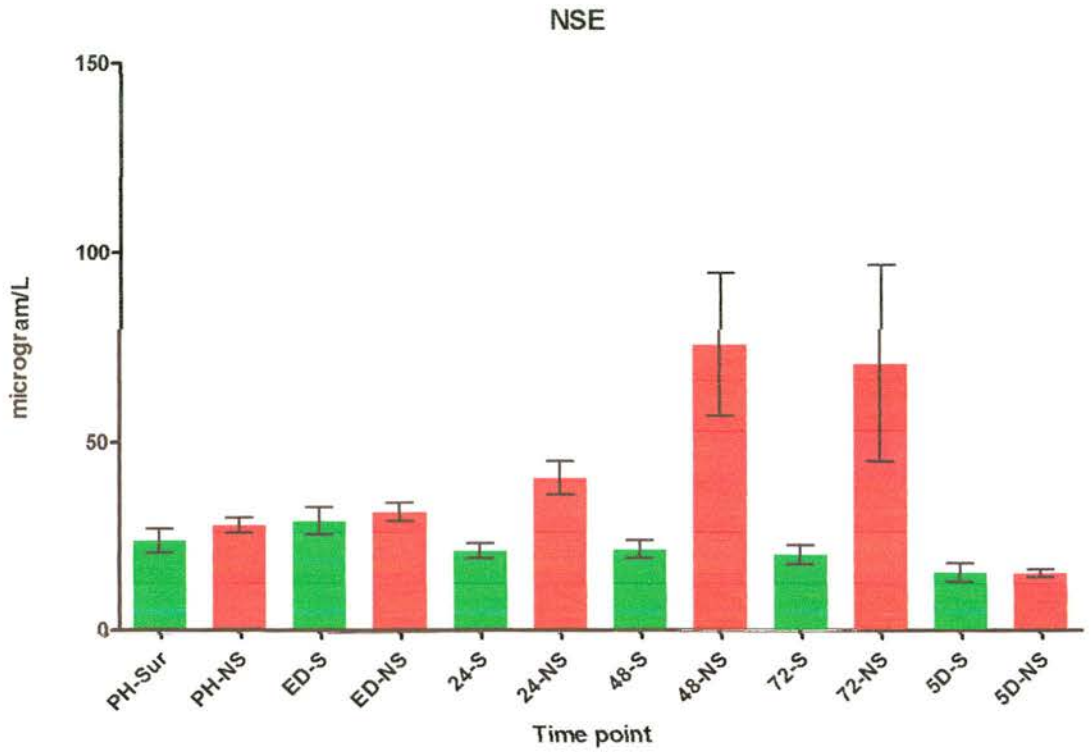
Figure 7.3. Serum neuron-specific enolase in patients who achieved ROSC *following* OHCA



In patients who achieved ROSC, there did not appear to be significant differences between survivors and non-survivors in the levels of NSE during the pre-hospital or ED phase, as shown in Figure 7.4. At 24-hours post-ROSC there appeared to be a significant difference in the serum level of NSE between survivors and non-survivors (21.1 vs 40.4 mcg/L, p=0.0005). This difference became more marked at 48-hours post-ROSC. At 5-days post-ROSC there was no difference in NSE levels between survivors and non-survivors.

Figure 7.4. Serum neuron-specific enolase in patients who achieved ROSC following OHCA

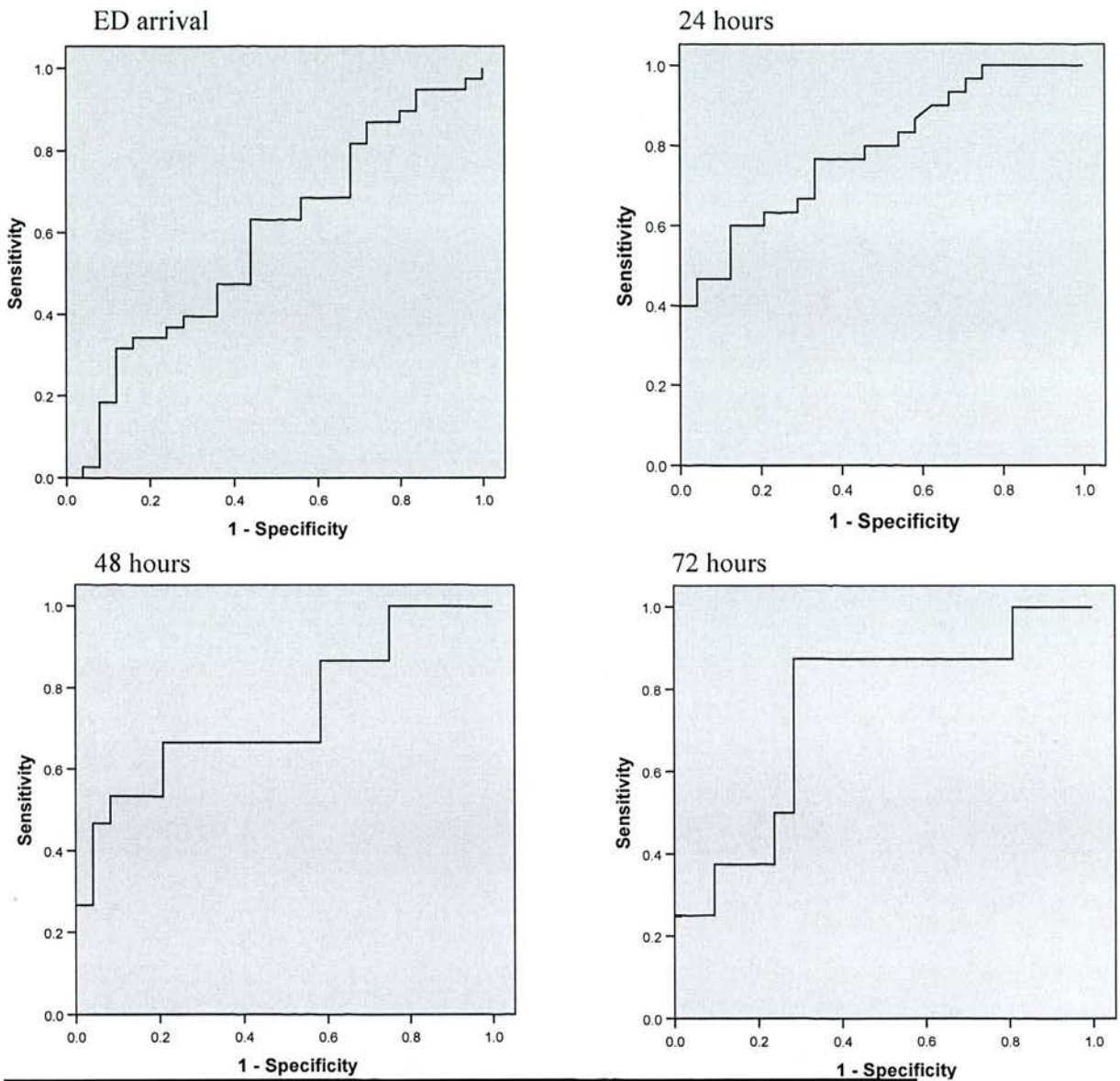
Green/S=survived to hospital discharge; Red/NS=non-survivor, died in ICU; PH=pre-hospital; ED=Emergency Department; 24=24-hours post-ROSC; 5D=5-days post-ROSC. Error bars= standard error of the mean.



7.5 Neuron specific enolase as a predictive marker of outcome following OHCA

In order to determine the value of NSE as a predictive marker between those who die in ICU and those who survive to discharge ROC curves have been produced and are presented in Figure 7.5, along with a table summarising the area under curve (AUC). The absolute cut-off value to predict mortality with 100% accuracy was 90 μg/L on arrival in the ED and 43.3 μg/L 24-hours post-ROSC.

Figure 7.5. Receiver operator characteristic curves and area-under-curve for NSE as a predictor of in-hospital mortality in patients who achieve ROSC following OHCA



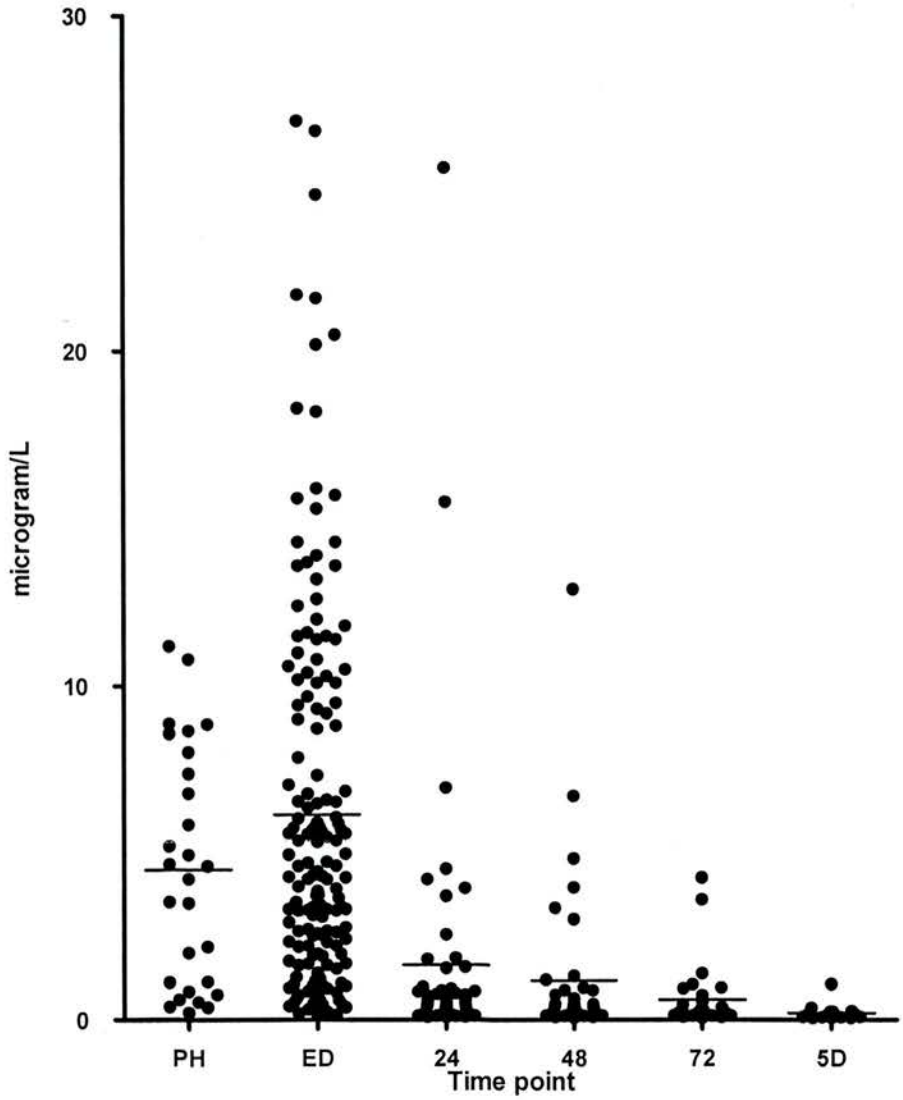
	Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
ED arrival	.581	.074	.279	.436	.726
24 hours	.787	.060	.000	.668	.905
48 hours	.742	.086	.012	.574	.910
72 hours	.750	.104	.040	.546	.954

a Under the nonparametric assumption, b Null hypothesis: true area = 0.5

7.6 S100b post-OHCA

Serum levels of S100b post-OHCA appeared to be raised in the immediate period following OHCA. The progression of S100b post-OHCA for all patients is shown in Figure 7.6.

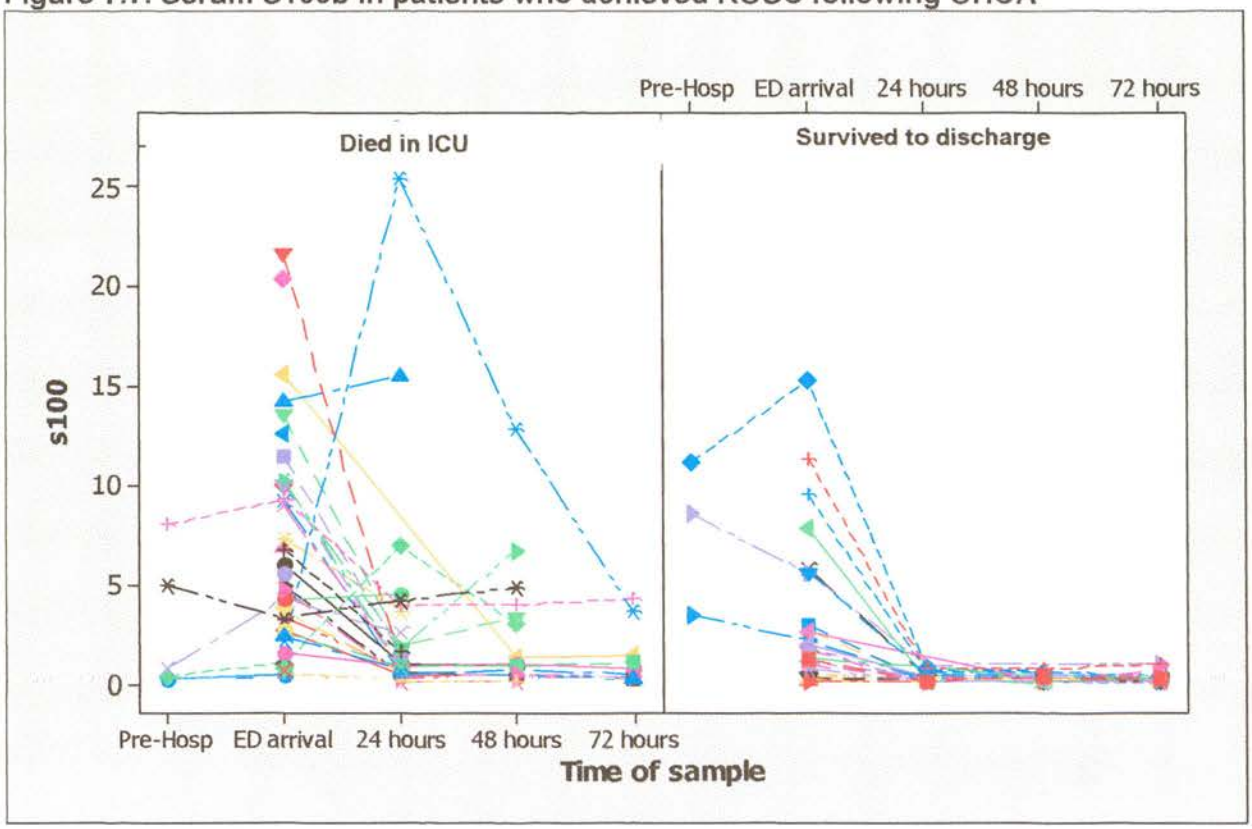
Figure 7.6 S100b post-OHCA for all patients
PH= pre-hospital; ED=Emergency Department; 24=24 hours post-OHCA; 5D= 5 days post-OHCA; Horizontal line depicts sample mean.



7.7 S100b post-OHCA in survivors versus non-survivors

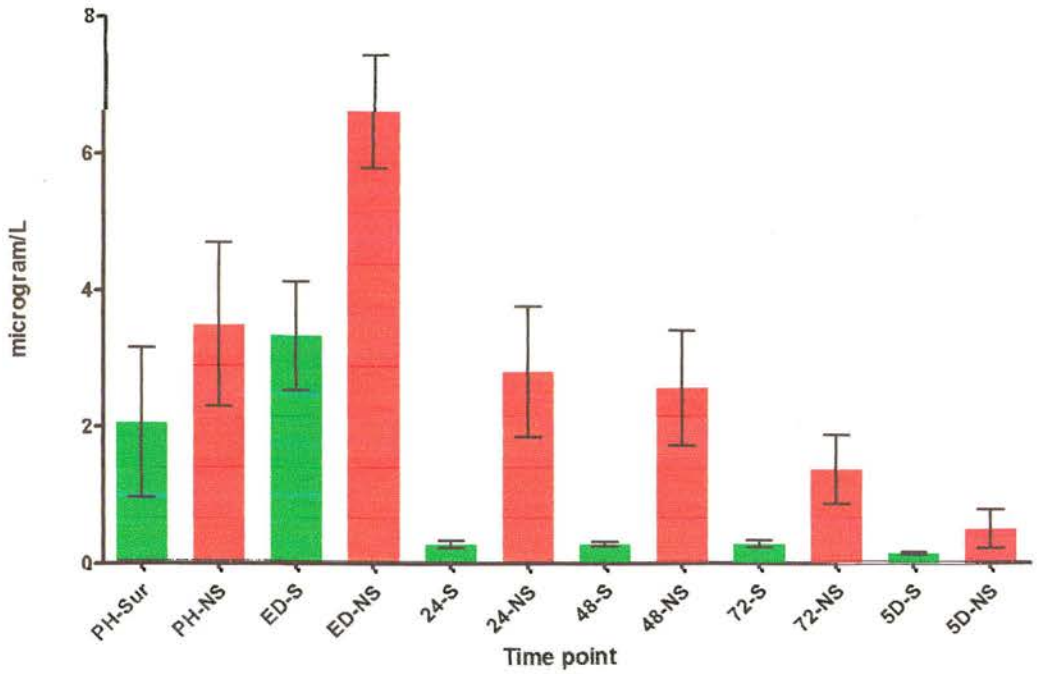
Post-OHCA patients who survived to hospital discharge had decreasing levels of S100b over the first 72-hours post-ROSC compared to patients who achieved ROSC but died in ICU, as shown in Figure 7.7

Figure 7.7. Serum S100b in patients who achieved ROSC following OHCA



There appeared to be a more marked difference in S100b levels between survivors and non-survivors, as shown in Figure 7.8. Whilst there was no significant difference during the pre-hospital phase, on arrival in the ED survivors had significantly lower levels of serum S100 when compared to non-survivors (3.3 vs 6.2 mcg/L, p=0.009). This difference persisted at all sampling points. The serum level of S100b in non-survivors decreased from 24-hours to 5-days following ROSC.

Figure 7.8. Serum S100b in patients who achieved ROSC following OHCA
Green/S=survived to hospital discharge; Red/NS=non-survivor, died in ICU; PH=pre-hospital; ED=Emergency Department; 24=24-hours post-ROSC; 5D=5-days post-ROSC. Error bars= standard error of the mean.

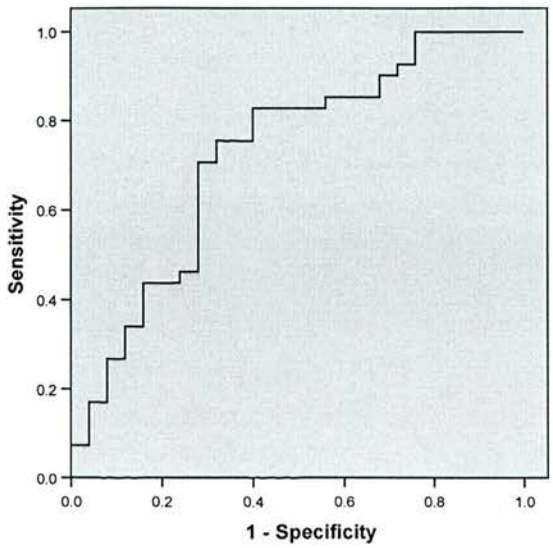


7.8 S100b on arrival in the ED as a predictive marker of outcome following OHCA

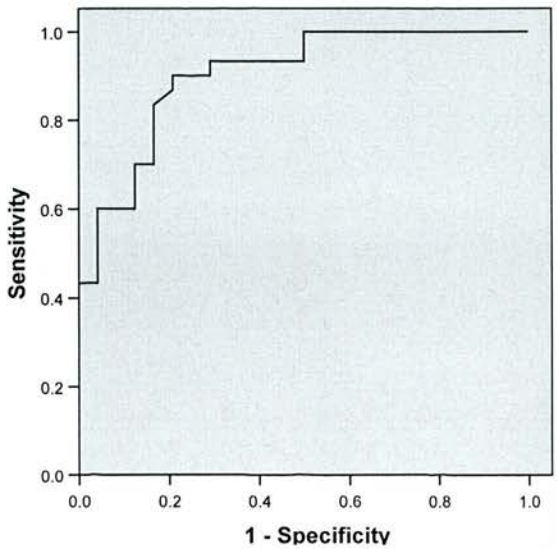
In order to determine if there is a cut-off point where we can distinguish between those who die in ICU and those who survive to discharge ROC curves have been produced and are presented in Figure 7.9 here along with a table summarising the area under curve (AUC). The absolute cut-off value to predict mortality with 100% accuracy was 15.4 μg/L on arrival in the ED and 0.96 μg/L 24-hours post-ROSC.

Figure 7.9. Receiver operator characteristic curves and area-under-curve for S100b as a predictor of in-hospital mortality in patients who achieve ROSC following OHCA

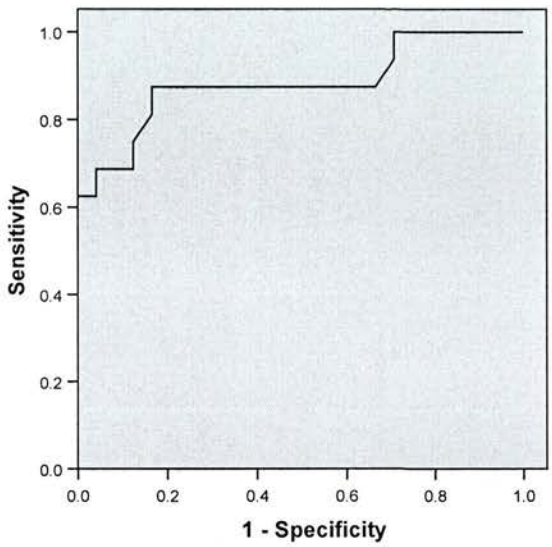
ED arrival



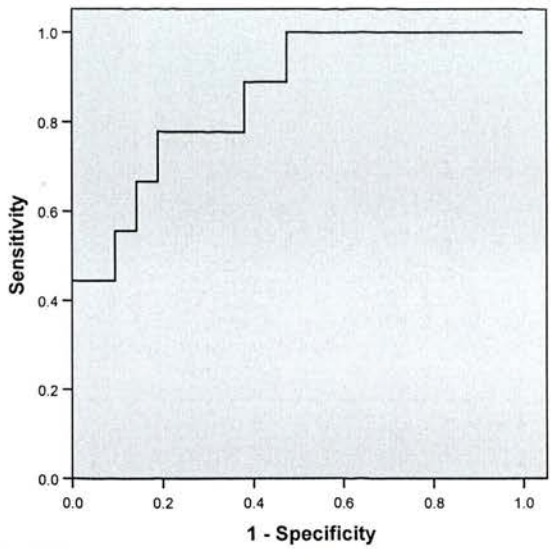
24 hours



48 hours



72 hours



	Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
ED arrival	.725	.066	.002	.595	.855
24 hours	.902	.041	.000	.822	.982
48 hours	.883	.061	.000	.763	1.003
72 hours	.857	.071	.002	.717	.997

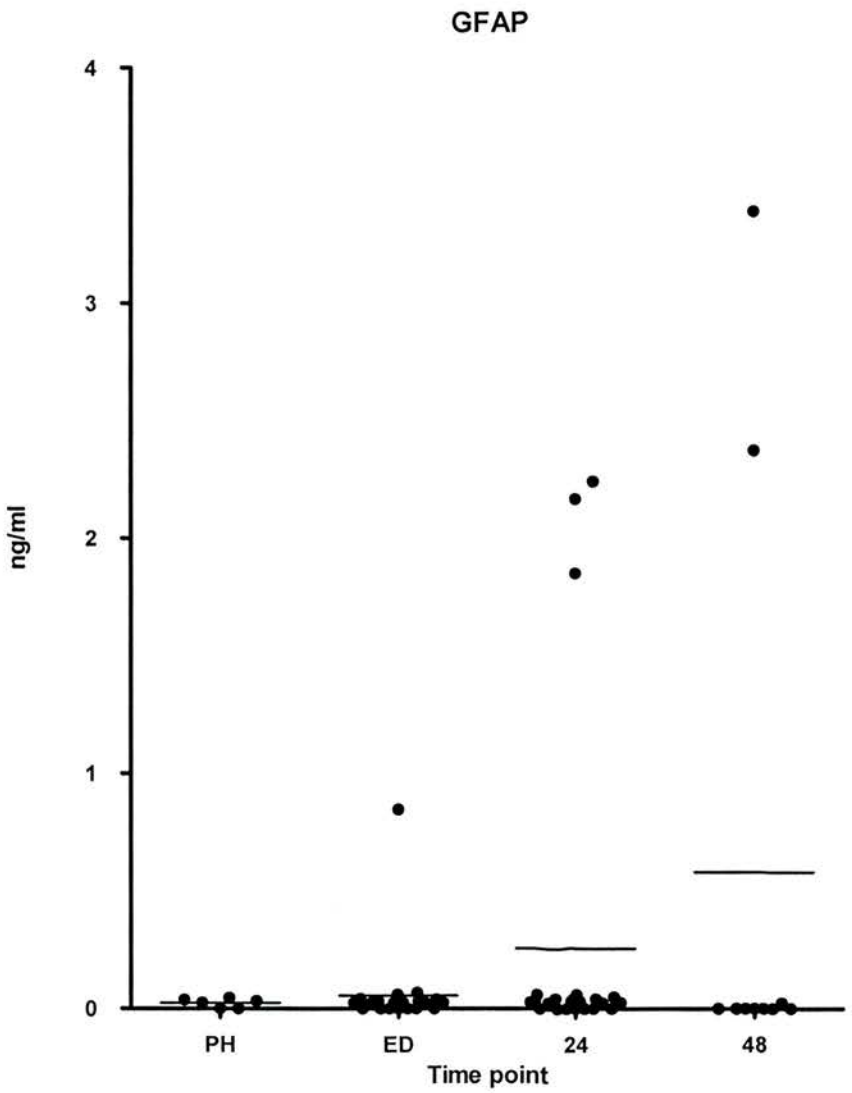
a Under the nonparametric assumption b Null hypothesis: true area = 0.5

7.9 Glial Fibrillary Acidic Protein post-OHCA

Only a limited number of GFAP assays were available. GFAP was measured in a total of 38 patients. Only time points up to and including 48-hours were measured.

The results of the GFAP assay for all patients are shown in Figure 7.10. Most of the results are below the limit of detection of the Biovendor ELISA assay (0.045 ng/ml).

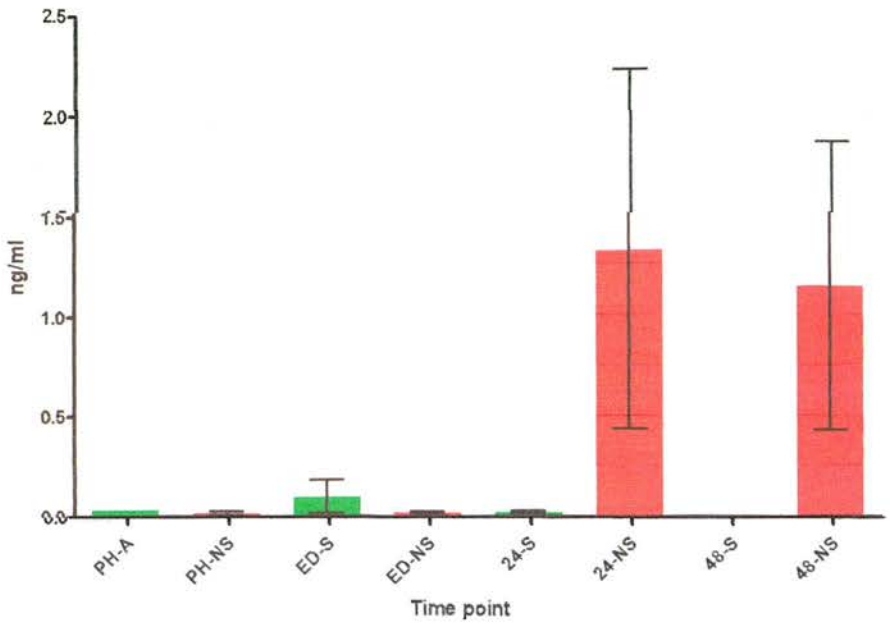
Figure 7.10 GFAP post-OHCA for all patients (n=38)
PH= pre-hospital; ED=Emergency Department; 24=24 hours post-OHCA; 5D= 5 days post-OHCA; Horizontal line depicts sample mean.



Non-survivors appeared to have detectable levels of GFAP at 24- and 48-hours post-ROSC, compared to survivors who had levels of GFAP below the limit of detection at all time points. This is shown in Figure 7.11.

Figure 7.11. Serum GFAP in patients who achieved ROSC following OHCA with VF as the initial rhythm

Green/S=survived to hospital discharge; Red/NS=non-survivor, died in ICU; PH=pre-hospital; ED=Emergency Department; 24=24-hours post-ROSC; Error bars= standard error of the mean.



7.10 GFAP as a prognostic marker following OHCA

In this select group of patients, GFAP was poor at predicting in-hospital mortality in patients who survived to ICU-admission. The AUC-ROC was 0.65 (95% CI 0.44-0.86).

7.11 Summary of brain injury markers post-OHCA

NSE, S-100b and GFAP were all raised in patients post-OHCA. Non-survivors showed significantly raised levels S-100 from the ED and NSE from 24-hours compared with survivors. S-100b measured at 24-hours post-ROSC is better than GFAP or NSE at 24-hours, or any time point, at predicting in-hospital mortality.

Given the limitations of our sampling points, brain injury markers appear to peak at different times. S-100b peaks within hours of ROSC, whereas NSE peaks, predominantly in non-survivors, several days post-ROSC. Virtually all patients showed decreasing absolute values of S-100b and NSE between the ED and 24-hour time point, the period during which cooling occurs.

Chapter 8

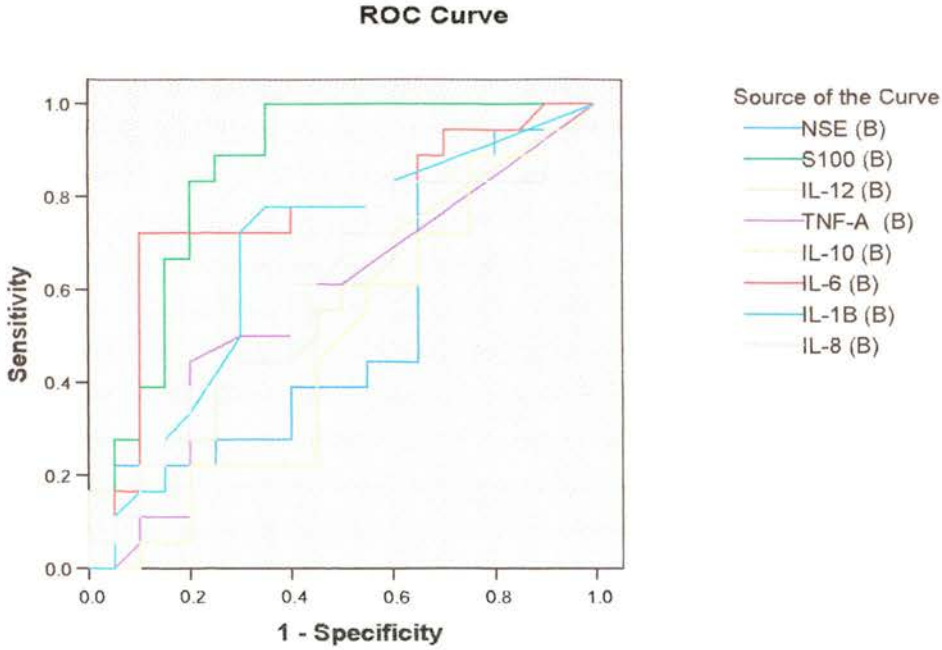
Results – Prognostication following OHCA

8.1 Prognostication on arrival in the ED

Prognostication is important following OHCA to allow rationalisation of on-going treatment, aid decisions regarding admission to ICU, select patients for novel therapies and more accurately inform relatives. We chose to evaluate S100, NSE and cytokines as predictive markers of survival to discharge following OHCA. We took samples on arrival to the ED and every 24 hours thereafter as these are the routine times for blood sampling in clinical practice. We evaluated the efficacy of S100, NSE and cytokines as predictive markers using ROC curves. Figure 8.1 shows the ROC curve to predict in-hospital mortality for both brain injury markers and markers of systemic inflammation on arrival at the ED. S100 and IL-6 have the highest area under the ROC curve, as shown in Table 8.1, although no single marker predicts in-hospital mortality with sufficient accuracy for clinical use. NB: GFAP assays were performed after the prognostic modelling was undertaken and are therefore not included in this chapter.

Figure 8.1 – ROC curve for predicting in-hospital mortality following OHCA on arrival in the ED

ROC curve predicting in-hospital mortality in OHCA patients who achieved ROSC pre-hospital. Markers of brain injury (NSE, S100) and markers of systemic inflammation (IL1β, IL-6, IL-8, IL-10, IL-12, TNF-α) are presented at time point B (arrival in the Emergency Department).



Diagonal segments are produced by ties.

Table 8.1 AUC-ROC – arrival in ED
Area under the ROC curve for markers of brain injury and markers of systemic inflammation on arrival in the ED.

Test Result Variable(s)	Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NSE (B)	.506	.097	.953	.315	.696
S100 (B)	.850	.066	.000	.720	.980
IL-12 (B)	.578	.094	.413	.394	.762
TNF-A (B)	.574	.095	.438	.387	.760
IL-10 (B)	.474	.096	.781	.286	.661
IL-6 (B)	.757	.084	.007	.592	.921
IL-1B (B)	.671	.090	.072	.494	.848
IL-8 (B)	.599	.094	.299	.414	.783

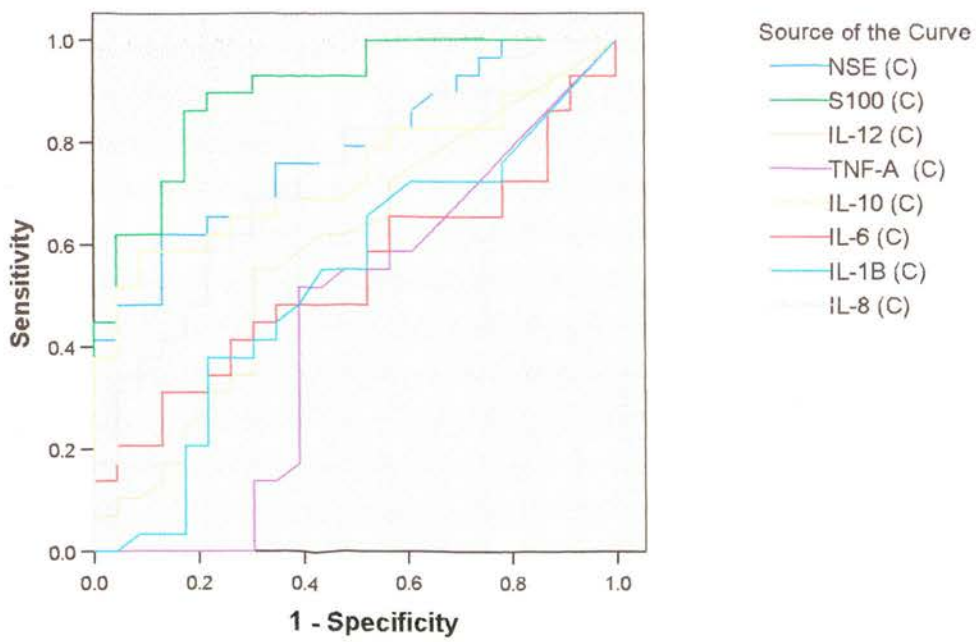
a Under the nonparametric assumption

b Null hypothesis: true area = 0.5

8.2 Prognostication 24-hours post-ROSC

Figure 8.2 shows the ROC curve to predict in-hospital mortality for both brain injury markers and markers of systemic inflammation at 24-hours post-ROSC. S100 has the highest area under the ROC curve, as shown in Table 8.2.

Figure 8.2 ROC curve for predicting in-hospital mortality following OHCA at 24-hours post-ROSC
ROC curve predicting in-hospital mortality in OHCA patients who achieved ROSC pre-hospital. Markers of brain injury (NSE, S100) and markers of systemic inflammation (IL1β, IL-6, IL-8, IL-10, IL-12, TNF-α) are presented at time point C (24-hours post-ROSC).



Diagonal segments are produced by ties.

Table 8.2 Area under the ROC curve for markers of brain injury and markers of systemic inflammation at 24-hours post-ROSC.

Test Result Variable(s)	Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NSE (C)	.782	.062	.001	.660	.904
S100 (C)	.901	.041	.000	.820	.982
IL-12 (C)	.592	.080	.257	.435	.750
TNF-A (C)	.442	.085	.478	.276	.609
IL-10 (C)	.736	.070	.004	.599	.873
IL-6 (C)	.537	.081	.652	.379	.695
IL-1B (C)	.531	.082	.699	.370	.693
IL-8 (C)	.735	.069	.004	.599	.870

a Under the nonparametric assumption

b Null hypothesis: true area = 0.5

8.3 Prognostic modelling

In order to perform logistic regression, the serum markers were log transformed and the results from the univariate analysis used [chi-squared tests for categorical data and two-sample t-test for continuous data] and included those variables which were statistically significant and those who were close [$p<0.1$]. Table 8.3 shows the results of the univariate analysis.

Table 8.3. Univariate analysis of factors predicting in-hospital mortality for patients who achieved ROSC following OHCA.

	Died ICU n=47	Mean (SD)	Survived to discharge n=27	Mean (SD)	Difference in means	95% CI for difference	p-value
Sex - Male	28 (60%)		20 (73%)				0.249
Bystander CPR	24 (51%)		17 (63%)				0.32
Rhythm - VF/VT	22 (47%)		25 (92%)				<0.001
Core temp ED		34.53 (1.34)		34.97 (1.34)	-0.45	(-1.34, 0.25)	0.201
Age		60.7 (18.8)		59.5 (12.3)	1.2	(-6.40, 8.81)	0.753
Downtime (mins)		33.5 (17.2)		18.1 (14.7)	15.5	(6.60, 24.38)	0.001
Log (NSE)		3.4 (0.5)		3.2 (0.5)	0.12	(-0.15, 0.38)	0.384
log (S100)		1.5 (1.0)		0.5 (1.4)	1.05	(0.41, 1.69)	0.002
log (IL12)		1.9 (0.9)		2.0 (0.7)	-0.13	(-0.69, 0.44)	0.654
log (TNFα)		1.4 (0.4)		1.6 (0.9)	-0.24	(-0.82, 0.33)	0.379
log (IL10)		2.2 (1.3)		2.2 (1.4)	0.02	(-0.73, 0.78)	0.949
log (IL6)		4.0 (1.7)		2.9 (1.3)	1.12	(0.31, 1.93)	0.008
log (IL1β)		1.2 (0.9)		1.1 (0.8)	0.12	(-0.41, 0.64)	0.654
log (IL8)		4.3 (1.5)		3.7 (0.9)	0.6	(-0.07, 1.28)	0.079

Using only the results available at the time of arrival in the ED the initial model contained log(S100), log(IL8), log (IL6), down time (in minutes) and rhythm (VF/VT versus the rest). After removing a single variable and re-running the model and repeating this until the only variables remaining were statistically significant a predictive model was developed From the patients admitted to ICU, as downtime increases and also log (S100) so did the odds of death in ICU [odds ratio (95% CI), 1.06 (1.01, 1.12), 3.43 (1.50, 7.82) per unit increase in downtime and log(S100) respectively].

Chapter 9

Results – Pre-hospital Resuscitation

9.1 Pre-hospital OHCA calls

Survival from OHCA is dependent on prompt intervention by pre-hospital emergency medical services (Atwood, 2005). In Scotland, this role is performed by the Scottish Ambulance Service (SAS). The SAS aims to be on-scene within 8 minutes of receiving a possible OHCA-call. The quality of resuscitation delivered by ambulance crews will influence survival. Transthoracic impedance (TTI) measurement is a useful tool in the assessment of the quality of pre-hospital resuscitation by ambulance crews (Olasveengen, 2007; Stecher, 2008c). The TTI signal is already recorded through the pads of the defibrillator used by the SAS (LIFEPAK 12) without the need for any further equipment to be placed on the patient. Both chest compressions and ventilations result in identifiable changes in the TTI trace. Analysing the trace using proprietary software (Codestat, Physio Control) allows a variety of resuscitation metrics including the hands-on-the chest time, compression rate and time-to-shock intervals to be accurately measured.

During the study period the Scottish Ambulance Service responded to 414 cardiac arrest calls within the study region.

The research doctor (RL) was called by the Emergency Medical Dispatch Centre (EMDC) 180 times. Details of the time of call and initial triage code is shown in Appendix X – "Log of calls to TOPCAT from EMDC". On 40 occasions RL was stood down en-route to-scene or the call was not appropriate to attend. RL attended the scene on 140 occasions. Full resuscitation was attempted in 47 cases.

9.2 Clinical interventions performed by the research doctor

The primary aim of the doctor being on-scene was to collect temperature data and blood samples. However, clinical care of the patient was the first priority. The research doctor gave advice regarding resuscitation technique or decisions to move the patient in 25 (44%) cases where resuscitation was attempted. The commonest directions to ambulance crew were to increase the proportion of time performing chest compressions, decrease compression rate

and use the defibrillator in manual mode to reduce the interval to deliver a shock. In 10 cases the ambulance crew wanted to extricate the patient before ROSC was achieved. Advice was given to continue resuscitation at-scene and ROSC was achieved in 7 of these cases.

In 16 cases the attending ambulance crew requested the doctor to intubate the patient and in 40 attempted-resuscitation cases the doctor was requested to gain intravenous access.

9.3 Quality of cardiopulmonary resuscitation performed by ambulance crews

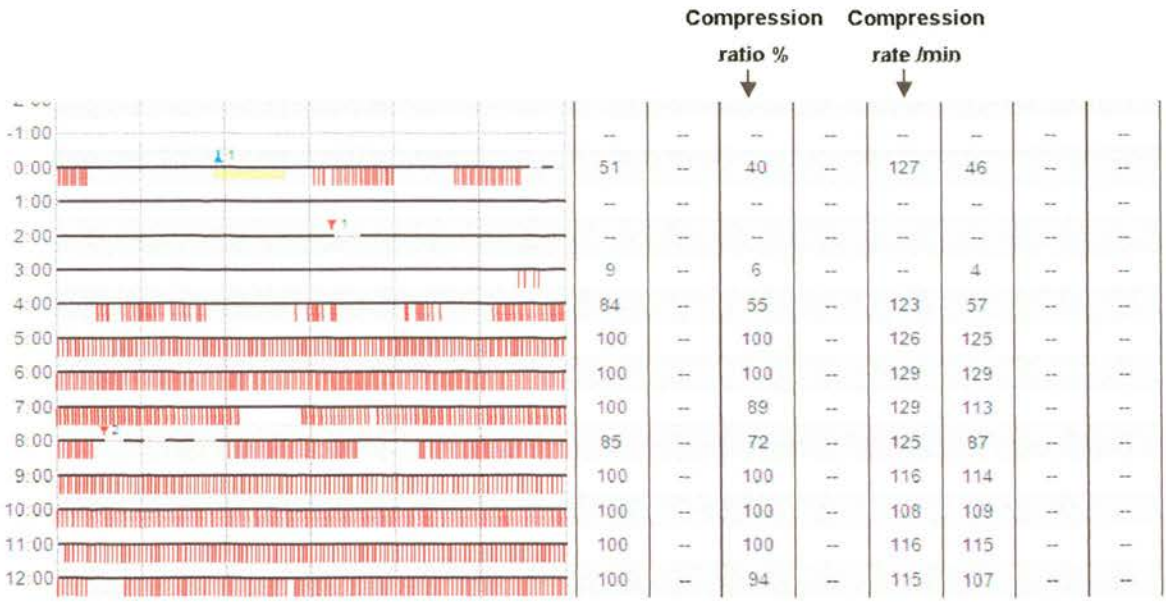
The quality of pre-hospital cardiopulmonary resuscitation performed by ambulance crews, as witnessed by the research doctor, was found to be variable. Clinical interventions not previously shown to improve outcome from OHCA (endotracheal intubation, intravenous cannulation and resuscitation drug administration) were frequently performed by ambulance crews in preference to performing good quality cardiopulmonary resuscitation. The quality of pre-hospital CPR was measured in several cases by downloading the trans-thoracic impedance trace from the Lifepak 12 defibrillator and using proprietary software (Codestat, Physio Control) to analyse CPR.

Having a doctor on-scene influenced the ambulance crews' CPR performance in several cases. Figure 9.1 shows a report generated by Codestat software demonstrating the effect of a having a doctor on-scene of a particular cardiac arrest case (Patient number 179).

Figure 9.1 Effect of having a doctor on-scene at the OHCA (witnessed collapse, 72 year old male in ventricular fibrillation)

Vertical numbers represent report time line (in minutes) from placing of defibrillator pads on patient. Each red line represents a single chest compression. A red triangle shows a DC shock. The compression rate of each minute and compression rate of each minute are shown.

The ambulance crew arrive and place defibrillator pads on the patient at Minute=0. Few chest compressions are performed in the first 3 minutes of resuscitation. The defibrillator is used in semi-automatic advisory mode to deliver a shock with a prolonged off-the-chest interval (>2 minutes). The research doctor arrives on scene at minute 5 and gives the attending ambulance crew advice on resuscitation technique. Subsequent to minute 5, the compression ratio increases, the compression rate decreases and the time off the chest to deliver a shock is markedly reduced.



9.4 Acceptance of a doctor on-scene of OHCA

After a resuscitation attempt at which the research doctor was on-scene, 60 ambulance members were sent an email inviting them to complete an online questionnaire. 47 (78%) responses were received. The full survey results are shown in Appendix VI – "Ambulance crew perceptions of a pre-hospital doctor at the scene of out-of-hospital cardiac arrest".

All (100%) of ambulance crews felt the doctor had integrated well with the pre-hospital team.

9.5 The effect of a pre-hospital doctor on ambulance crew performance

42 (89%) ambulance staff felt reassured by the doctor's presence. 16 (34%) ambulance staff felt their own clinical performance improved after the doctor arrived on-scene. 2 (4%) ambulance staff felt the doctor hindered their usual clinical work. 44 (94%) ambulance staff felt the doctor gave them useful feedback during or after the resuscitation attempt.

Several of the surveyed ambulance crews made comments on the value of having a pre-hospital doctor on-scene for education, performing clinical interventions and decision making – as shown in Appendix VI.

9.6 Outcome

The research doctor was on-scene for 47 OHCA cases where full resuscitation was attempted. ROSC was achieved in 24 (51%) of cases compared to when the research doctor was not present 87 of 189 (46%) achieved ROSC (p=0.62).

There was a trend towards higher survival to discharge when the research doctor was present (8/47 (17%) vs. 19/189 (10.0%), p=0.20).

9.7 Summary – Pre-hospital doctor at OHCA-scene

The quality of pre-hospital resuscitation performed by ambulance crews was found to be variable. The pre-hospital doctor frequently intervened during resuscitation to perform clinical and non-clinical intervention. A pre-hospital doctor on-scene of an OHCA is accepted by ambulance crew, who particularly value on-scene education and reassurance.

Chapter 10

Discussion

10.1 Core body temperature following OHCA – study findings

In this study we found that oesophageal temperature follows a predictable pattern in the first few minutes and hours after OHCA. Patients cooled quickly in the pre-hospital phase and remained cool in transit to the ED. Thereafter, patients destined to survive to discharge appeared to re-warm faster before cooling was commenced and took longer to reach target temperature. Patients maintained oesophageal temperature close to the target range for MTH throughout the pre-hospital phase without specific intervention to lower temperature. Possible explanations for this finding are given below.

Several studies have previously noted episodes of hyperthermia occurring in patients following cardiac arrest (Kamarainen, 2009; Uray, 2008) but our study reports a correlation between early changes in oesophageal temperature within the normothermic range and patient survival. The reason for this observation remains uncertain. In line with previous studies (Kamarainen, 2008a; Uray, 2008), we noted a significant difference in the time between collapse and ROSC between survivors and non-survivors. Longer collapse-ROSC times are likely to be associated with greater neurological injury and impairment of central mechanisms of body temperature control.

10.2 Core body temperature post-OHCA – comparison to published literature

Our study has demonstrated that patients remain cool (Mean=33.7°C, 95% CI 32.8-34.5) in the pre-hospital phase of OHCA. Transfer-to-hospital times in the City of Edinburgh are generally short (<15 minutes) with total pre-hospital time usually <60 minutes. Patients post-OHCA may have little time to re-warm during the pre-hospital phase.

Animal evidence has shown that a delay in initiating cooling negates the beneficial effect of MTH after cardiac arrest (Carroll, 1992; Coimbra, 1994; Kuboyama, 1993), yet there is currently limited human evidence to support immediate cooling. For early MTH to be achieved in human cardiac arrest, cooling would need to begin in the pre-hospital phase. To

date, no human trials have shown pre-hospital cooling per se improves survival from OHCA (Kamarainen, 2009; Kim, 2009), although pre-hospital intra-nasal cooling has recently been shown to be safe and effective at inducing hypothermia (Castren, 2010) and further clinical trials are on-going.

Despite the paucity of clinical evidence demonstrating benefit (Kamarainen, 2009; Kim, 2007), some ambulance services have adopted methods of initiating hypothermia in the pre-hospital phase (Suffoletto, 2008). Cooling at the scene or during transport requires additional equipment, resources and monitoring and may distract from the basic practice of maintaining a patent airway, ventilation and adequate circulation. Further research is currently underway to establish whether pre-hospital cooling really confers additional benefit. A recently published study from Australia failed to demonstrate survival benefit by cooling pre-hospital with cold saline (Bernard, 2010), although intra-arrest evaporative nasal cooling looks promising in the pre-hospital setting (Band, 2008; Castren, 2010).

10.3 Core body temperature post-OHCA – possible mechansims

The reason for OHCA survivors re-warming quickly post-ROSC and being more difficult to cool remains uncertain. Patients who survive to hospital discharge may have better cardiac function following ROSC and less hypothalamic damage, leading to a higher oesophageal temperature as a function of greater cardiac output and intact thermoregulation. Several (n=28) non-survivors had severe neurological injury as their eventual cause of death and all remained hypothermic after ROSC. Animals studies have shown that ischaemic brain injury can result in hypothalamic damage and body temperature lability (He, 1999).

The temperature gradient between the brain and the rest of the body may be important. Measuring absolute brain temperature is technically difficult (Axelrod, 2006). Whilst we measured oesophageal temperature, known to be an accurate measurement of central blood temperature (Shiraki, 1986), the absolute brain temperature may be different. Further research is warranted, possibly using high-resolution neuro-imaging, to quantity the relationship between absolute brain and body temperature, especially during cooling.

Body temperature lability – episodes of both hyperpyrexia and spontaneous hypothermia - have recently been shown to be adversely linked to outcome in patients following in-hospital cardiac arrest (Suffoletto, 2009). The mechanism for this is unknown though there are similarities to the temperature dysregulation found in severe sepsis (Adrie, 2004). In sepsis,

development of spontaneous hypothermia is associated with greater neurological injury (Clemmer, 1992) although animal work suggests that controlled MTH may improve outcomes (Taniguchi, 2003).

10.4 Core body temperature monitoring – study limitations

This study should be interpreted in the context of certain limitations. Whilst we observed several statistically significant results, data was collected from a relatively small number of patients in a single centre. We did, however, achieve a high degree of data capture on all patients enrolled in the study. Body temperature was recorded using oesophageal probes with instructions given to insert the probe to 15cm from the nostril. It could be argued that, placing these probes in the field or in the ED may have resulted in probes not being inserted to adequate length and sitting in the posterior nasopharynx. This may have altered temperature recordings slightly, however there was strong pre-hospital agreement in temperature in all patients. The oesophagus is an accurate site to measure body temperature, second only to the pulmonary artery, and is more robust than other techniques commonly used in our setting (e.g. tympanic membrane temperature using an infrared probe) (Axelrod, 2006; Craig, 2002). Oesophageal temperature monitoring is also the most practical means of accurately measuring body temperature during the pre-hospital phase of patient care.

10.5 Therapeutic hypothermia – future research

Several questions regarding the use of MTH remain unanswered (Nolan, 2008). The optimum time, or time window, following OHCA when cooling should commence remains under investigation. Recent studies have explored the possibility of initiating cooling during CPR (Castren, 2010), with initial results being promising. The optimal timing for initiating MTH after OHCA is unclear. There is limited animal evidence suggesting that early initiation of cooling is beneficial (Kuboyama, 1993; Sterz, 1991; Zhao, 2008). There is no direct human clinical evidence to support the immediate initiation of cooling, although retrospective analysis has indicated a possible benefit to patients cooled shortly after ROSC (Wolff, 2009). Several studies have examined the possibility of pre-hospital cooling (Kamarainen, 2008a; Kamarainen, 2008b) but prospective randomised clinical trials have, so far, failed to demonstrate any survival benefit (Kamarainen, 2009; Kim, 2007). Further human clinical studies are required to establish whether such early cooling confers outcome benefit.

The optimum therapeutic target temperature has yet to be established. The TOPCAT study has demonstrated patients re-warm post-ROSC, possibly due to restoration of circulation but also possibly driven by a pro-inflammatory response. It is possible that maintaining normothermia alone post-ROSC may be sufficient to prevent pro-inflammatory reperfusion injury and may confer equal benefit in terms of outcome.

The maintenance and re-warming phases remain under investigation, although we have not specifically examined these in the TOPCAT study.

In our study, cooling was initiated approximately 2 hours after ROSC, on arrival on the ICU. If MTH is not commenced in patients following OHCA, many patients develop a mild pyrexia commencing around 8 hours after ROSC (The Hypothermia after Cardiac Arrest Study Group, 2002). Hyperthermia following OHCA has previously been associated with poor outcome (Zeiner, 2001). Episodes of pyrexia are correlated with poorer neurological outcome in focal ischaemic brain injury, and measures are taken to actively keep these patients normothermic (Hajat, 2000). Pyrexia after OHCA may reflect a pro-inflammatory cytokine-mediated response to the whole body ischemia-reperfusion insult during resuscitation (Takino, 1991). It is postulated that this inflammatory response may cause multi-organ injury and, in particular, exacerbate neurological injury. Because the mechanism of the benefit accrued from MTH is uncertain it is difficult to build a physiological rationale for the optimum target temperature for therapeutic hypothermia. It is unclear whether it is tissue cooling per se, (with reduction in oxygen demand and modulation of tissue injury pathways) improves outcome, or whether the attenuation of specific elements in the inflammatory response to OHCA is also crucially important. It is possible that maintenance of normothermia with immune-modulation and other strategies for neuroprotection post-ROSC could provide similar benefits to whole body cooling (Bouch, 2008).

It is uncertain whether cooling the brain, heart, whole body or all three is important when using MTH. It is unclear whether cooling with surface techniques, intra-nasally or with cold intravenous fluids differentially cools different organs, possible affecting outcome. An understanding of these concepts will be needed to optimise MTH as a therapy for post-OHCA patients.

10.6 Core Body Temperature - Conclusion

Following OHCA all patients have oesophageal temperatures below normal in the pre-hospital phase and on arrival in the ED. Patients who achieve ROSC following OHCA and survive to hospital discharge are warmer on arrival in ICU and take longer to reach target MTH temperatures compared to patients who die in hospital. The reason for the robust association between oesophageal temperature and survival from OHCA remain unclear and further research is warranted to clarify this relationship.

10.7 Inflammation post-OHCA - findings

We have shown that serum inflammatory markers are raised in OHCA patients post-ROSC. Both pro- and anti-inflammatory cytokine production was up-regulated post-OHCA, indicating global activation of the inflammatory cascade. Serum levels of IL-6, IL-8, IL-10 and IL-12 differ between survivors and non-survivors and have different rates of progression. TNF-α and IL-1β are also raised but no difference was observed between survivors and non-survivors. The fact we did not identify specific peaks of TNF-α and IL-1β may be a reflection of the timing of blood sampling and cytokine clearance. A peak level occurring in the first 12-hours post-ROSC may remain undetected by sampling at 24-hours. IL-8 has previously been shown to peak at 12-hours post-ROSC (Ito, 2001), however we chose 24-hours to coincide with routine clinical sampling. Similar to previous studies (Shyu, 1997), we did not find a correlation between cardiovascular status post-ROSC and the magnitude of the post-ROSC inflammatory response.

The early (pre-hospital, ED and 24-hour) level of IL-6 observed in patients in the TOPCAT study was comparable to patients in septic shock (Adrie, 2004), indicating a significant level of cytokinaemia. IL-6 is known to propagate a pro-inflammatory response and also acts on the thermocentres of the hypothalamus resulting in pyrexia. Interestingly, one human study has suggested MTH leads to increased IL-6 production and whilst still conferring therapeutic benefit (Diestel, 2008). Clearly, more research is warranted to examine the role and effect of individual cytokines.

We have shown that neutrophil activation post-OHCA occurs earlier than described in some other previous studies (Adrie, 2004), with neutrophil activation being detectable in the CPR-phase of resuscitation.

There have been previous suggestions that catecholamines, both endogenous and exogenous, play a role in leucocyte activation and propagation (Springer, 1995). We did not observe a difference in serum elastase levels in patients who had varying quantities of adrenaline administered during resuscitation. We found survivors of OHCA had less adrenaline administered during resuscitation than non-survivors. This is likely to reflect the shortened resuscitation period as adrenaline has recently been shown not to improve survival OHCA in humans (Olasveengen, 2009a).

10.8 The role of systemic inflammation post-OHCA

Cytokinaemia is present after OHCA, both in survivors and non-survivors. There were significant differences in levels of IL-8 and IL-10 in survivors and non-survivors of OHCA, however no global correlation was observed between systemic inflammation and core body temperature. There are two possible explanations for these findings. Firstly, amelioration of the systemic inflammatory response mediated by cytokines is not required for the therapeutic benefit of hypothermia. Secondly, the inflammatory response and post-ROSC reperfusion cascades occurring in the brain may differ from those in the rest of the body.

Neutrophils are activated and increase in number during cardiopulmonary resuscitation, as shown by the increased cell surface marker expression and increased serum levels of human neutrophil elastase. In animal models leucocytes are thought to play a role in early microcirculatory reperfusion failure through leucocyte adherence and sticking (Bottiger, 2002). Neutrophils, activated by the cytokine cascade, can then migrate across the blood-brain barrier leading to further brain injury (Schmid-Schonbein, 1993). Human studies have shown similar results to ours, with neutrophil activation indicated through increased levels of neutrophil elastase, complement split products and soluble intercellular adhesion molecules present post-resuscitation (Bottiger, 2002; Lechleitner, 1993; Mussack, 2001).

The systemic inflammatory response following OHCA may be different from the response observed in other proinflammatory conditions such as sepsis or stroke. In bacterial infection, inflammatory cytokines may cause circulatory failure by increasing capillary permeability, vasodilation, mitochondrial dysfunction and disseminated intravascular coagulation (Richards, 2005). Secondary neutrophil activation following stroke can lead to secondary neurological injury (Bhardwaj, 2003).

Following cardiac arrest, cerebral ischaemia results in a complex cascade of events, triggered by hypoxia and depletion of energy stores, leading to cellular depolarisation and calcium influx that result in excitotoxic cell death. The magnitude of cerebral injury is dependent on the time between onset of cerebral ischaemia and restoration of circulation and the duration and severity of ischaemic injury (Harukuni, 2006). Post-ischaemic inflammation plays a role in brain ischaemia (Kriz, 2009). Following the onset of cerebral ischaemia, cytokines act on the vascular endothelium to increase the expression of intercellular adhesion molecule-1, E-selectin and P-selectin, which promotes neutrophil adherence and accumulation (Huang, 2006). We have demonstrated that neutrophil activity in the serum is increased in the immediate stage following OHCA. Expression of these integrins, together with structural changes in the basal lamina and extracellular matrix results in the migration of neutrophils across the endothelium. Activated neutrophils bind to endothelial ligands, migrating to the area of tissue injury. Neutrophil adhesion is a critical step in vascular endothelial injury, resulting in increased microvascular permeability and thrombosis (Homer-Vanniasinkam, 1997). Secondary inflammatory cascades occur leading to further cerebral ischaemia. Reducing the brain temperature below 34°C can reduce inflammatory cell infiltrate and reduce concentrations of a variety of inflammatory mediators such as reactive oxygen species, nitric oxide and inflammatory cytokines (Yenari MA, 2005). However, serum levels of inflammatory cytokines measured in the acute phase of ischaemic stroke do not correlate with lesion size or outcome (Intiso, 2004; Sanchez-Moreno, 2004). It is possible, therefore, that the beneficial effect of therapeutic hypothermia maybe related to restricted modulation of inflammation in the brain.

A previous study has demonstrated that, despite cooling, post-OHCA patients had a significant rise in IL-6 levels during the hypothermic period (Fries, 2009). In the setting of acute ischaemic stroke, IL-6 is associated with neurological deterioration (Vila, 2000). TNF-α has also been implicated in secondary brain injury following OHCA but it remains unclear whether cytokines per se lead to brain injury or whether they act as a catalyst for other cellular responses, such as neutrophil migration, which ultimately cause brain injury.

MTH has previously been shown to result in lower levels of TNF-α after OHCA (Fries, 2009). Using specifically targeted therapies, such as infliximab for TNF-α, could alleviate the adverse effect of pro-inflammatory mediators. Infliximab has been shown to reduce myocardial dysfunction following cardiac arrest in a swine model (Niemann, 2010). Other targeted anti-cytokine therapies using monoclonal antibodies have been shown to reduce

tissue injury following reperfusion in animal models (Sekido, 1993). Targeted anti-inflammatory therapy could prevent brain injury if the precise mechanisms of the reperfusion syndrome were better understood.

10.9 Cytokines post-OHCA – comparison of our findings with published literature

Previous studies have demonstrated a measurable inflammatory response in the hours following ROSC (Adrie, 2002; Adrie, 2004; Ito, 2001; Zacharia, 2009) and animal models have shown that MTH reduces cytokine release from the brain following cardiac arrest (Meybohm, 2010b). We have demonstrated that a systemic inflammatory response is occurring in the immediate post-ROSC phase, with cytokinaemia and neutrophil activation occurring in the pre-hospital phase. The systemic inflammatory response appears greater in patients that do not survive. However, no definite evidence exists to show that the systemic inflammatory response observed post-ROSC causes secondary neurologic or systemic injury (Adrie, 2002; Grunenfelder, 2000). The magnitude of the inflammatory response is likely to be related to the severity and duration of global ischaemia and reperfusion.

Cardiac arrest leads to whole body ischaemia. The effect of hypoperfusion on organs other than the brain is important. Gut ischaemia can lead to translocation of exotoxins through sites of gut wall ischaemia and elevated endotoxin levels have been described within 2 days following successful resuscitation (Adrie, 2002). Bacteraemia from the gut may also contribute to systemic inflammation (Cerchiari, 1993). In addition, gastric aspiration is common in cardiac arrest and even when minimal, can give rise to a systemic inflammatory response (Gaussorgues, 1988).

Animal studies of proinflammatory cytokines post-OHCA have shown IL-6 and TNF-α to rise within one hour of ROSC but to return to normal levels within 24 hours (Sipos, 2010). The same study found that different levels of hypothermia did not unequally influence the amount of circulating proinflammatory cytokines. However, IL-10 mRNA levels were found to have prognostic power for survival. We have seen very similar results in our human study.

Therapeutic hypothermia is believed to decrease the inflammatory response (Fries, 2009). An in vitro study demonstrated that moderate hypothermia reduced the inflammatory response of stimulated microglia cells, shown by a reduction in inflammatory cytokine

production and reduced expression of adhesion molecules (Schmitt, 2007). A previous study has also shown hypothermia decreases some proinflammatory cytokines but increased IL-6 production from stimulated endothelial cells (Diestel, 2008). Our findings are consistent with the hypothesis that MTH modulates the inflammatory response following OHCA but it remains under investigation whether a reduction in inflammatory response has beneficial effects in terms of survival and neurological outcome.

10.10 Inflammation post out-of-hospital cardiac arrest – future research

A major difficulty in evaluating systemic inflammation post-OHCA is determining whether it is a marker of therapeutic efficacy, potential therapeutic target or not related to post-ROSC brain injury.

An animal model is required to test hypotheses on elements of the inflammatory process after cardiac arrest. The impact of modifying leucocyte activity and cytokinaemia following cardiac arrest needs to be evaluated. A previous animal study demonstrated improved neurological outcome in dogs treated with a simple anti-inflammatory (Ibuprofen) following cardiac arrest (Kuhn, 1986). An animal model could be used to label neutrophils during cardiac arrest, track their migration and activity and observe the outcome of modifying neutrophil activity. An animal model of depleted neutrophils and other leucocytes would determine whether these cells are firstly involved in secondary brain injury following cardiac arrest and, secondly, whether therapeutic hypothermia exerts neuroprotection by altering neutrophil activity. Similarly, the pro-inflammatory response could be pharmacologically manipulated and the effect on outcome observed.

If ROSC is achieved following OHCA, the effect of whole body ischemia and reperfusion leads to a state known as the "post-resuscitation syndrome". This is characterized by hyperthermia, hypotension and multiple organ failure and is a likely consequence of whole-body ischaemia/reperfusion injury that occurs following ROSC (Adrie, 2004; Nolan, 2008). The effect of the reperfusion syndrome may be more detrimental than the initial primary ischaemic insult (Ar'Rajab, 1996), particularly leading to secondary brain injury. Although reperfusion is essential for survival, it may exacerbate cerebral injury and thus presents a treatment paradox (Safar, 2002).

A targeted approach to post-ROSC resuscitation care is required, combining therapeutic hypothermia with haemodynamic optimization (Gaieski, 2009; Sunde, 2007). The exact

elements of the post-resuscitation syndrome that are detrimental are unknown, but the inflammatory response has been suggested as having harmful secondary effects. Greater understanding of the post-resuscitation syndrome is crucial if targeted protective therapies are to evolve.

10.11 Brain injury markers post-OHCA

Serological markers of brain injury are a potential means of prognostication following OHCA. Studies have demonstrated the difficultly in using early markers of brain injury to predict outcome (Song, 2010). We found S-100 to be superior to NSE and GFAP in predicting outcome from OHCA in the context of patients treated with MTH. Our results are consistent with previously published studies, evaluating S100 prior to the use of MTH (Hachimi-Idrissi, 2002; Martens, 1996; Rosen, 1998). We found the cut-off value for poor outcome to be 0.96 μg/L at 24-hours post-ROSC which is in-keeping with other studies (Shinozaki, 2009b).

This is one of the few studies to evaluate GFAP as a predictive neurological marker following OHCA, but we found it to be poor compared with S-100. A previous study found when serum GFAP was present in the serum at >0.1ng/dL in the context of MTH when measured at 48-hours post-ROSC, poor outcome was accurately predicted. However, GFAP levels measured at 12 or 24 hours post-ROSC were not significantly associated with outcome (Kaneko, 2009).

Our failure to show any correlation between core body temperature and serum markers of neurological injury may be multi-factorial. A gradient may exist between brain temperature and the oesophageal suggest there is a gradient between brain and body temperature is indicative of neurological injury, or neurological injury is prevented by the cooling process of MTH and not related to core body temperature prior to cooling being initiated.

10.12 Pre-hospital resuscitation practice

During the TOPCAT study, the quality of pre-hospital resuscitation was noted, by direct observation and analysis of defibrillator downloads to be variable. The commonest observed findings were poorly performed chest compressions, inappropriate early tracheal intubation and intravenous cannulation, and use of the defibrillator in semi-automatic mode. Several recent studies have reported the adverse physiological consequences of poor resuscitation

technique (Frenneaux, 2003) and have demonstrated that quality of pre-hospital CPR influences outcome from OHCA (Christenson, 2009a; Garza, 2009).

Chest compressions aim to provide adequate perfusion to the vital organs during cardiac arrest. Periods during which chest compressions are not performed result in lack of blood flow – defined as no blood flow time (NBT). Recent clinical evidence shows increased NBT during CPR is associated with poor outcome (Christenson, 2009b).

A variety of factors influence the delivery of effective chest compressions. Tracheal intubation and obtaining intravenous access for subsequent drug delivery interrupt chest compressions, but no high level evidence exists to show that either intervention improves survival from OHCA in humans (Kramer-Johansen, 2006; Olasveengen, 2009a). Automated rhythm analysis will often take longer than manual rhythm interpretation by a trained healthcare professional, resulting in increased delay-to-shock times when ambulance defibrillators are used in automatic mode (Kramer-Johansen, 2007a; Yu, 2002). Calculating the NBT has important implications for resuscitation training, optimising the quality of resuscitation and clinical outcome after OHCA (Stecher, 2008b).

There have been calls for regular monitoring of CPR quality and for uniform reporting of CPR variables (Kramer-Johansen, 2007b). Ambulance crews receive initial training in performing CPR pre-hospital but receive variable training updates. Individual crews are likely to encounter few OHCA and skill retention can be problematic (Perkins, 2009). There is a need to monitor compliance of CPR performed by ambulance crews in accordance with current international resuscitation guidelines (Olasveengen, 2007), as previous investigation of pre-hospital practice has demonstrated poor compliance with recommended chest compression depth and rate, compounded by pauses in delivery of chest compressions (Steen, 2008; Wik, 2005). Determining the quality of pre-hospital resuscitation performed by ambulance crews in the field is technically difficult, but crucial if pre-hospital care of OHCA patients is to improve (Olasveengen, 2009b).

The results from our survey of ambulance personnel suggest they value the presence of an experienced clinician at the scene of OHCA, particularly for education, feedback and to aid clinical decision making. The pre-hospital physician/paramedic model is widely employed in continental Europe and Scandinavia. The TOPCAT study has shown that resuscitation practice can be changed with simple advice and guidance.

10.13 Pre-hospital resuscitation future research

Towards the end of the TOPCAT study period (November 2009), a pilot study was launched with the aim of improving pre-hospital resuscitation practice by ambulance crews. Transthoracic impedance (TTI) measurement is a useful tool in the assessment of the quality of pre-hospital resuscitation by ambulance crews (Olasveengen, 2007; Stecher, 2008a). The TTI signal is already recorded through the pads of many models of external defibrillator without the need for any further equipment to be placed on the patient. Both chest compressions and ventilations result in identifiable changes in the TTI trace.

Logging and analysis of TTI data from ambulance defibrillators after OHCA does not yet occur routinely in the United Kingdom. The ICECAP (Informed Continuous Education of Cardiac Arrest for Ambulance Personnel) pilot study is the first of its kind in the UK to implement a data network to collect defibrillator TTI data via telemetry from ambulances in the City of Edinburgh, Scotland. Following each resuscitation attempt, the attending ambulance crew selected the respective case and instructed the defibrillator to transmit the data. After receipt of the TTI trace, CODESTAT software was used to calculate the no-flow ratio, compression rate and time interval to administer defibrillatory shocks. A resuscitation report was generated that was printed and sent as part of feedback and training to the attending ambulance crew.

From the initial 58 TTI traces received, the mean ratio of chest compressions was 73% (95% CI 69-77%), the mean chest compression rate was 128 (95% CI 122-134). There were 19 resuscitation attempts where at least once shock was administered from the defibrillator. The mean time interval to deliver to deliver a shock was 27 seconds (95% CI 22-32s)

The ICECAP pilot study has started a monthly resuscitation class at Edinburgh City ambulance station and, together with feeding back the resuscitation reports, aims to achieve a measurable improvement in resuscitation practice in the City of Edinburgh.

Chapter 11

Conclusion

The TOPCAT study has investigated the physiological response to OHCA and current resuscitation practice in Scotland.

The physiological response to OHCA has been characterised in relation to oesophageal temperature, systemic inflammation and serum markers of brain injury. Following OHCA all patients have oesophageal temperatures below normal in the pre-hospital phase and on arrival in the ED. Patients who achieve ROSC following OHCA and survive to hospital discharge are warmer on arrival in ICU and take longer to reach target MTH temperatures compared to patients who die in hospital. The mechanisms of action underlying oesophageal temperature and survival from OHCA remain unclear and further research is warranted to clarify this relationship.

A systemic inflammatory response occurs earlier in the post-ROSC phase than previously described. Further research is warranted to clarify the mechanism of action of therapeutic hypothermia post-OHCA and the role of the systemic inflammatory response in determining survival. S100b is a more reliable predictor of outcome following OHCA than NSE or GFAP. The TOPCAT study has generated several testable hypotheses for future work.

The quality of pre-hospital and in-hospital resuscitation in Scotland have been examined. MTH is commonly used in Scottish ICUs but rarely commenced in the ED. The quality of pre-hospital resuscitation is variable and practice can be improved. We have demonstrated the value of a second tier, experienced pre-hospital response to OHCA calls. Following the TOPCAT study, initiatives have been launched aiming to improve the quality of pre-hospital resuscitation practice in Edinburgh.

Appendix I

Published papers

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Clinical paper

Esophageal temperature after out-of-hospital cardiac arrest: An observational study☆

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ABSTRACT

Introduction: Out-of-hospital cardiac arrest (OHCA) is a significant cause of death and severe neurological disability. The only post-return of spontaneous circulation (ROSC) therapy shown to increase survival is mild therapeutic hypothermia (MTH). The relationship between esophageal temperature post OHCA and outcome is still poorly defined.

Methods: Prospective observational study of all OHCA patients admitted to a single centre for a 14-month period (1/08/2008 to 31/09/2009). Esophageal temperature was measured in the Emergency Department and Intensive Care Unit (ICU). Selected patients had pre-hospital temperature monitoring. Time taken to reach target temperature after ROSC was recorded, together with time to admission to the Emergency Department and ICU.

Results: 164 OHCA patients were included in the study. 105 (64.0%) were pronounced dead in the Emergency Department. 59 (36.0%) were admitted to ICU for cooling; 40 (24.4%) died in ICU and 19 (11.6%) survived to hospital discharge. Patients who achieved ROSC and had esophageal temperature measured pre-hospital ($n = 29$) had a mean pre-hospital temperature of 33.9 °C (95% CI 33.2–34.5). All patients arriving in the ED post OHCA had a relatively low esophageal temperature (34.3 °C, 95% CI 34.1–34.6). Patients surviving to hospital discharge were warmer on admission to ICU than patients who died in hospital (35.7 °C vs 34.3 °C, $p < 0.05$). Patients surviving to hospital discharge also took longer to reach T_{targ} than non-survivors (2 h 48 min vs 1 h 32 min, $p < 0.05$).

Conclusions: Following OHCA all patients have esophageal temperatures below normal in the pre-hospital phase and on arrival in the Emergency Department. Patients who achieve ROSC following OHCA and survive to hospital discharge are warmer on arrival in ICU and take longer to reach target MTH temperatures compared to patients who die in hospital. The mechanisms of action underlying esophageal temperature and survival from OHCA remain unclear and further research is warranted to clarify this relationship.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a significant cause of death and severe neurological disability across Europe. Resuscitation is attempted in 66 per 100,000 population annually.[1] Despite efforts to optimise early access to advanced cardiac life support, survival rates from OHCA remain low, with survival to hospital discharge rates varying from less than 5% to over 10%.[2,3] Good quality cardiopulmonary resuscitation and prompt defibrillation are key interventions to achieve return of spontaneous circulation (ROSC) and neurologically intact survival. Following ROSC the aim is to limit further brain injury and minimise subsequent morbidity and mortality. The only post-ROSC therapy shown to increase survival and improve neurological outcome following OHCA is mild therapeutic hypothermia (MTH).

In 2002 two prospective randomised trials found that inducing MTH (32–34 °C) after OHCA could increase survival and reduce neurological morbidity.[4,5] Both trials had similar recruitment criteria and included patients with ROSC who remained intubated and ventilated after OHCA due to ventricular fibrillation (VF) of presumed cardiac aetiology. Despite the uniformity of study groups, the implementation of MTH differed significantly between the two trials.

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2010.03.017

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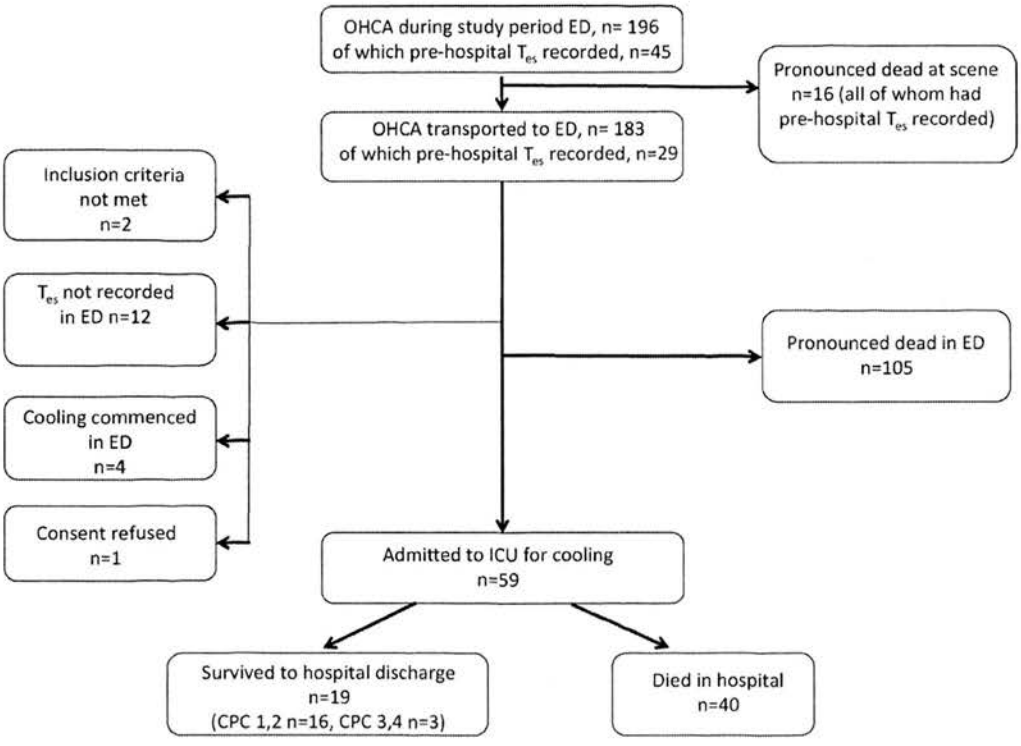

Fig. 1. Patient flow diagram.

In 2003, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) published an advisory statement indicating that further research was required to establish the optimum target temperature, optimal duration of hypothermia, rates of cooling and re-warming and an understanding of the mechanism of MTH.[6] This call for further research was reiterated by ILCOR in 2007.[7] To generate explanatory hypotheses answering some of these important clinical questions baseline observational data is required. Establishing the pattern of change of body temperature after OHCA will inform decisions about the most effective time to commence cooling and may enhance understanding of the mechanisms of MTH.

This prospective study aims to describe the natural progression of esophageal temperature following OHCA from the pre-hospital phase until arrival on the Intensive Care Unit (ICU) and observe any relationship between esophageal temperature, outcome and time to reach target temperature.

2. Methods

We prospectively collected data on OHCA in the Edinburgh area (population approximately 500,000) over a 14-month period (1st of August 2008 to 31st September 2009). OHCA patients transported to the Emergency Department (ED) of a single university teaching hospital (Royal Infirmary of Edinburgh) were enrolled in the study. Inclusion criteria were adult cardiac arrest of non-traumatic cause, unwitnessed by ambulance personnel and who remained comatose after ROSC. The study was approved by the Scottish national medical research ethics committee.

The Scottish Ambulance Service routinely collect Utstein template data on all OHCA patients. Time of emergency call, ambulance dispatch and on-scene times are recorded automatically by the ambulance service computer system with the aid of real-time satellite positioning. Ambulance records were matched with the ED and ICU patient notes. Patients were followed up to the point of discharge from the admitting hospital or death. Cerebral Performance Category[8] was noted at the point of hospital discharge.

For a proportion of the OHCA episodes studied, a research doctor (RL) attended the scene with an ambulance crew. For these patients esophageal temperature (T_{es}) measurement was commenced in the field. All other OHCA patients had esophageal temperature measuring commenced on arrival in the ED. Esophageal temperature monitoring is the most practical means of accurately measuring core body temperature during the pre-hospital phase of patient care. An esophageal temperature probe was marked at 15 cm from the tip and inserted as soon as practical during the resuscitation. The thermometer tip was therefore 15 cm from the nostril and the position confirmed by laryngoscopy. The probe was linked to a digital recording thermometer (DataTherm II) with esophageal temperature recorded every 10 min to 0.1 °C accuracy. Esophageal temperature recording continued for a 24-h period.

We recorded the pattern of change in esophageal temperature from either the pre-hospital or ED phase of the OHCA patient's journey until target temperature ($T_{targ.} < 34$ °C) was reached in the ICU. Time taken to reach $T_{targ.}$ after ROSC was recorded, together with time to admission to the ED and ICU and the time active cooling was commenced.

The study was approved by the Scottish National Research Ethics Committee. Consent from the next-of-kin was sought until the patient was able to give informed consent. If the patient did not survive, permission was granted from the Ethics Committee to use the research data.

In the receiving hospital, cooling is routinely initiated after admission to the ICU. Body surface cooling (Arctic Sun, Medivance Ltd) is used with automatic temperature feedback control. In a small proportion of cases cooling is commenced in the ED by placing ice packs on the patient. Patients who had active cooling initiated in the ED were excluded from the time point at which cooling was commenced. Data were entered into a database (Microsoft Access 2007) and analysed using statistical analysis software (Microsoft

Table 1
Out-of-hospital cardiac arrest (OHCA) patient demographics. CPR: cardiopulmonary resuscitation; VF: ventricular fibrillation; PEA: pulseless electrical activity; NS: not significant; ROSC: return of spontaneous circulation; and IQR: interquartile range.

	Died in hospital (%)	Survived to hospital discharge (%)	Significance
Number	40	19	–
Male sex	23 (57.5)	14 (73.7)	
Mean age (years)	61.7	59.4	NS
Witnessed OHCA	23 (57.5)	12 (63.2)	NS
Bystander CPR performed	19 (47.5)	9 (47.4)	NS
Initial cardiac rhythm			
VF/pulseless VT	19 (47.5)	16 (84.2)	$p = 0.016$
PEA	4 (10.0)	1 (5.3)	NS
Asystole	17 (42.5)	2 (10.5)	$p = 0.031$
Ambulance response time median (min)	8 (IQR 5-13)	6 (IQR 4-7)	NS
ROSC achieved pre-hospital	35 (87.5)	18 (94.7)	NS
Time from initial call to ROSC Mean (min:s)	29:02	13:46	$p = 0.0006$

Excel 2009, SPSS 16.0). Values in the survivor and non-survivor groups were compared at two time points (arrival in the ED and arrival on the ICU) using an unpaired *t*-test. Statistical significance was taken at the 95% level.

3. Results

During the study period 183 OHCA patients were transported to the ED. Of these, 29 patients had pre-hospital esophageal temperature measurements performed. Four patients had cooling commenced in the ED, either ice packs or cold IV fluid and were excluded after cooling commenced as they could not be compared to the rest of the study cohort. Two patients were excluded as they were not comatose on arrival. ED temperature data was not available for 12 patients, all of whom subsequently died in the ED. Temperature data was available to all patients admitted to ICU. One patient refused consent after discharge from ICU. Patient enrolment into the study is shown in Fig. 1. A total of 164 patients were enrolled into the study and all were followed up until hospital discharge or death. On arrival in the ED, one patient was noted to have the temperature probe situated next to the cuff of the endotracheal tube on direct laryngoscopy and the probe was re-sited. Otherwise no complications from temperature monitoring were observed.

105 (64.0%) patients were pronounced dead in the ED. 59 (35.6%) patients enrolled in the ED survived to admission to ICU and were eligible for inclusion. 19 (11.7%) enrolled patients survived to hospital discharge. 40 (25.0%) patients admitted to ICU subsequently died in hospital. Patient demographics and resuscitation details of survivors and non-survivors are shown in Table 1.

Patients who achieved ROSC and had esophageal temperature measured pre-hospital ($n = 29$) had a mean esophageal temperature of 33.9 °C (95% CI 33.2–34.5). All eligible patients arriving in the ED post OHCA ($n = 164$) also had a relatively low esophageal temperature (Table 2) but there was no significant difference in ED esophageal temperature between patients who died in hospital ($n = 40$) and patients surviving to hospital discharge ($n = 19$).

Table 2
Esophageal temperature of OHCA patients arriving in the Emergency Department (ED). T_{es}: esophageal temperature and ICU: Intensive Care Unit.

	Mean T_{es} on arrival ED	Standard deviation	95% CI of mean
All patients ($n = 164$)	34.3	1.59	34.1–34.6
Died in ED ($n = 105$)	34.1	1.70	33.8–34.5
Survived to ICU admission ($n = 59$)	34.4	1.37	34.0–34.9
Survived to hospital discharge ($n = 19$)	34.8	1.42	34.2–35.6

The majority of survivors had a favourable Cerebral Performance Score (CPC) at hospital discharge (CPC 1: $n = 8$, CPC 2: $n = 8$). Three survivors had poor neurological outcome at hospital discharge (CPC 3: $n = 2$, CPC 4: $n = 1$). 16 non-survivors who were admitted to ICU had severe, isolated, ischaemic brain injury (including three with brain stem death). All of these patients arrived in the ED cool (mean T_{es} 34.5 °C; 95% CI 33.7–35.3) and did not appear to re-warm prior to ICU admission (mean ICU admission T_{es} 34.2 °C; 95% CI 33.6–34.8).

Patients surviving to hospital discharge were warmer on admission to ICU than patients who survived to ICU admission but subsequently died in hospital. There was no significant difference from the time of ROSC to ICU admission in survivors and non-survivors (3 h 18 min vs 3 h 38 min, $p = 0.71$). Patients surviving to hospital discharge also took longer to reach T_{targ} (<34 °C) once cooling was commenced (Table 3). The progression of T_{es} post-ROSC is shown in Fig. 2.

4. Discussion

In this single centre observational study, we found that esophageal temperature follows a predictable pattern in the first few minutes and hours after OHCA. Patients in our study cooled quickly in the pre-hospital phase and remained cool in transit to the ED. Thereafter, patients destined to survive to discharge appeared to re-warm faster before cooling was commenced and took longer to reach target temperature, a finding not yet described in the literature. Esophageal temperature on arrival in the ED was 34.4 °C (range = 30.5–36.6 °C) – comparable to the target temperature reached in a recent pre-hospital pilot study of the feasibility of cooling post OHCA[9] and also previously published studies.[10,11] Patients in our study maintained esophageal temperature close to the target range for MTH throughout the pre-hospital phase without specific intervention to lower temperature. Despite the paucity of clinical evidence demonstrating benefit,[9,11] some ambulance services have adopted methods of initiating hypothermia in the pre-hospital phase.[12] Cooling at the scene or during transport requires additional equipment, resources and monitoring and may distract from the basic practice of maintaining a patent airway, ventilation

Table 3
Esophageal temperature on admission to the Intensive Care Unit (ICU) and time to reach target temperature. T_{es}: esophageal temperature; ROSC: return of spontaneous circulation; and T_{targ}: target therapeutic hypothermia of <34 °C.

	Died in hospital	Survived to hospital discharge	*p*-value
Mean T_{es} on arrival ICU	34.3 (95% CI 33.9–34.8)	35.7 (95% CI 35.2–36.3)	0.0008
Mean time from ROSC to arrival on ICU	159 min (95% CI 137–183)	169 min (95% CI 140–198)	0.60
Mean time from ROSC to T_{targ} (<34 °C)	219 min (95% CI 165–271)	320 min (95% CI 266–374)	0.019
Mean time from arrival ICU to T_{targ}	96 min (95% CI 56–136)	168 min (95% CI 118–217)	0.028

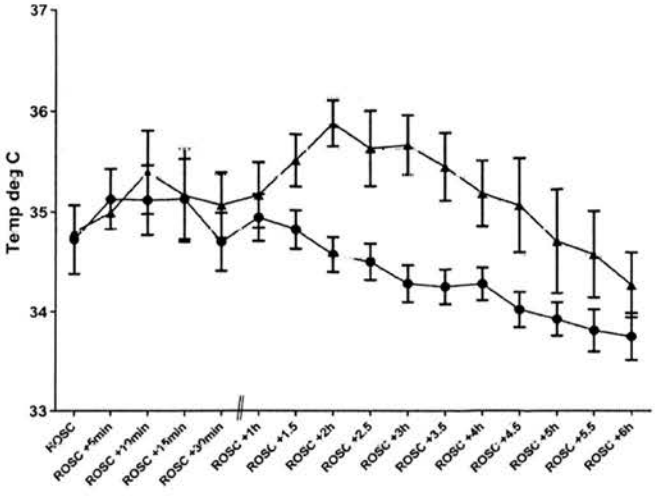

Fig. 2. Mean T_{es} of out-of-hospital cardiac arrest patients who achieved return of spontaneous circulation (ROSC) and survived to hospital discharge (triangles; $n = 19$) and patients who achieved ROSC, survived to Intensive Care Unit admission but died in hospital (dots; $n = 40$). Error bars represent standard error of the mean.

and adequate circulation. Further research is currently underway to establish whether pre hospital cooling really confers additional benefit. A North American study of outcome from cardiac arrest when cold IV fluids are infused in the pre-hospital setting is currently recruiting (http://www.ClinicalTrials.gov/identifier NCT00391469).

Several studies have previously noted episodes of hyperthermia occurring in patients following cardiac arrest but our study reports a correlation between early changes in esophageal temperature within the normothermic range and patient survival. The reason for this observation remains uncertain. We noted a significant difference in the time between collapse and ROSC between survivors non survivors. Longer collapse ROSC times are likely to be associated with greater neurological injury and impairment of central mechanisms of body temperature control.

Patients who survive to hospital discharge may have better cardiac function following ROSC and less hypothalamic damage, leading to a higher esophageal temperature as a function of greater cardiac output and intact thermoregulation. Several ($n = 16$) non-survivors had severe neurological injury as their eventual cause of death and all remained hypothermic after ROSC.

Body temperature lability – episodes of both hyperpyrexia and spontaneous hypothermia – have recently been shown to be adversely linked to outcome in patients following in-hospital cardiac arrest.[13] The mechanism for this is unknown though there are similarities to the temperature dysregulation found in severe sepsis.[14] In sepsis, development of spontaneous hypothermia is associated with greater neurological injury[15] although animal work suggests that controlled MTH may improve outcomes.[16]

The optimal timing for initiating MTH after OHCA is unclear. There is limited animal evidence suggesting that early initiation of cooling is beneficial.[17–19] There is no direct clinical evidence to support the immediate initiation of cooling, although retrospective analysis has indicated a possible benefit to patients cooled shortly after ROSC.[20] Several studies have examined the possibility of pre-hospital cooling[21,22] but prospective randomised clinical trials have, so far, failed to demonstrate any survival benefit.[9,11] A temperature rise >38 °C is often seen in patients following OHCA but it is unclear whether this bears any causal relationship to survival or neurological outcome, and the reason for this pyrexia is unknown.

In our study, cooling was initiated approximately 2 h after ROSC, on arrival on the ICU. If MTH is not commenced in patients following OHCA, many patients develop a mild pyrexia commencing around 8 h after ROSC.[4] Hyperthermia following OHCA has previously been associated with poor outcome.[23] Episodes of pyrexia are correlated with poorer neurological outcome in focal ischaemic brain injury, and measures are taken to actively keep these patients normothermic.[24] Pyrexia after OHCA may reflect a pro inflammatory cytokine-mediated response to the whole body ischaemia reperfusion insult during resuscitation.[25] It is postulated that this inflammatory response may cause multi-organ injury and, that in particular, exacerbate neurological injury. Because the mechanism of the benefit accrued from MTH is uncertain it is difficult to build a physiological rationale for the optimum target temperature for therapeutic hypothermia. It is unclear whether it is tissue cooling per se (with reduction in oxygen demand and modulation of tissue injury pathways) that improves outcome, or whether the attenuation of specific elements in the inflammatory response to OHCA is also crucially important. It is possible that maintenance of normothermia with immune-modulation and other strategies for neuroprotection post-ROSC could provide similar benefits to whole body cooling.[26] Further research is warranted to determine the mechanism by which MTH confers neurological protection and the optimum modality, timing and duration of cooling.

Our study should be interpreted in the context of certain limitations. Whilst we observed several statistically significant results, our data was collected from a relatively small number of patients in a single centre. We did, however, achieve a high degree of data capture on all patients enrolled in the study. Body temperature was recorded using esophageal probes with instructions given to insert the probe to 15 cm from the nostril. Placing these probes in the field or in the ED may have resulted in probes not being inserted to adequate length and sitting in the posterior nasopharynx. This may have altered temperature recordings slightly, however there was strong pre-hospital agreement in temperature in all patients. The esophagus is an accurate site to measure body temperature, second only to the pulmonary artery, and is more robust than other techniques commonly used in our setting (e.g. tympanic membrane temperature using an infrared probe).[27,28] Esophageal temperature monitoring is also the most practical means of accurately measuring body temperature during the pre hospital phase of patient care.

5. Conclusion

Following OHCA all patients have esophageal temperatures below normal in the pre hospital phase and on arrival in the ED. Patients who achieve ROSC following OHCA and survive to hospital discharge are warmer on arrival in ICU and take longer to reach target MTH temperatures compared to patients who die in hospital. The mechanisms of action underlying esophageal temperature and survival from OHCA remain unclear and further research is warranted to clarify this relationship.

Conflict of interest statement

The authors have no relationships with organisations that could inappropriately influence their work. The manuscript, data, tables and figures have not been submitted for publications elsewhere.

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EDITOR'S CHOICE

Therapeutic hypothermia in the emergency department following out-of-hospital cardiac arrest

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ABSTRACT

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality and severe neurological disability. Recent literature suggests that mild therapeutic hypothermia (MTH) can improve survival and neurological outcome in some groups of comatose patients after cardiac arrest but uncertainty exists over the best way to implement this treatment. This review examines the evidence for the efficacy and mode of implementation of MTH after OHCA, particularly in the Emergency Department setting. A literature search was performed and all systematic reviews; human and animal randomised and non-randomised trials were screened for inclusion. Specific emphasis was placed on MTH being commenced in the prehospital and Emergency Department setting. Outcome measures were: time to reach target temperature, in-hospital mortality, neurological outcome at hospital discharge and complications of therapeutic hypothermia. Two systematic reviews found that MTH improved outcome after OHCA. Five human randomised controlled trials were identified. Two trials commenced cooling prehospital. One showed a favourable outcome but the other failed to show survival benefit. The other three trials only commenced cooling after the patient arrived in hospital and all showed improved survival for patients treated with MTH after OHCA. Evidence from animal and non-randomised studies suggests cooling should be commenced as early as possible after return of spontaneous circulation. Cold intravenous fluid was reported as a safe, effective means of cooling in the emergency setting. MTH improves patient outcome after OHCA. There is some evidence to suggest cooling should be commenced early. Cold intravenous crystalloid infusion may be the preferred cooling method in the Emergency Department.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a leading cause of morbidity and mortality in the developed world. Resuscitation is attempted in 66 per 100 000 population across Europe every year. Of those that survive to leave hospital, >50% are left with permanent neurological sequelae.[1] The first clinical intervention in the postresuscitation phase of OHCA shown to decrease mortality and improve neurological outcome is mild therapeutic hypothermia (MTH).[2 3] MTH was used in patients with OHCA as early as 1950, but cooling was largely abandoned due to complications. The concept of preserving the brain in the field, protecting it from hypoxia until the patient could be transported to hospital for spontaneous circulation to be restored or placed on cardiopulmonary bypass, was first suggested by Peter Safar in 1984.[4 5] In the 1990s, a number of encouraging animal studies showed benefit, and several pilot human studies were conducted.[6 7] In 2002, two randomised trials demonstrated the benefit of cooling survivors of witnessed OHCA who had ventricular fibrillation (VF) as the presenting rhythm.[2 3] This led to the International Liaison Committee on Resuscitation, the American Heart Association and the European Resuscitation Council recommending MTH in the management of unconscious patients following OHCA.[8 9] Despite these recommendations, the use of MTH is not yet routine.[10] Since 2002, further trials have explored the use of MTH for non-VF OHCA, traumatic cardiac arrests and in paediatric patients.

The optimum initiation, method and duration of cooling are unclear.[11] Animal research suggests that cooling early after return of spontaneous circulation (ROSC) is associated with improved neurological outcome,[12 13] but human studies show that delayed cooling also yields favourable results.[3 12 14]

Both invasive and non-invasive cooling methods have been developed, and whole-body and brain-only cooling methods have been trialled. The majority of cooling techniques have been trialled in critical care settings with few methods specifically evaluated in the Emergency Department (ED).[15] While MTH initiated in the ED may reduce the time taken to reach target temperature, prehospital cooling poses logistical and technical challenges. Patients arriving at hospital after OHCA may require in-hospital transfer for imaging or cardiac intervention prior to ICU (intensive care unit) admission. Cooling techniques intended for early deployment must therefore combine efficacy with ease of use.

While some ambulance services and EDs have adopted MTH as a routine treatment for patients after OHCA, it is unclear whether the available evidence supports this practice.

This paper aims to review and discuss key elements of the published literature on using MTH in the emergency setting and is not intended to provide a definite statement in the form of a systematic review.

We reviewed the published literature to answer the following:

1. In comatose patients after OHCA, does MTH improve neurological outcome?
2. Is there an optimal time and place for commencing MTH?
3. In patients after OHCA considered for MTH, what methods of cooling are available for use within the ED?

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METHODS

A literature review was performed by a single investigator. All short-listed studies were assessed by the other two authors for quality and to ensure the inclusion criteria were met. Search terms included 'therapeutic hypothermia', 'hypothermia', 'cardiac arrest', 'heart arrest', 'out-of-hospital cardiac arrest' and 'cardiopulmonary resuscitation'. Outcome parameters included in-hospital mortality, 6-month mortality and favourable neurological outcome (defined as independent living) within 6 months.

Inclusion criteria were studies commencing cooling early post-ROSC. For human studies we included those commencing cooling prehospital or in the ED. For animal studies we included cooling before, during or immediately after cardiac arrest. Specific exclusion criteria included non-cardiac arrest conditions—for example, myocardial infarction, cerebrovascular accident and traumatic brain injury. In contrast to previous published systematic reviews,[16 17] this review specifically examines MTH use in the prehospital and ED setting. We found the number of randomised controlled trials (RCTs) on the use of MTH after OHCA to be small; therefore, all RCTs were screened for inclusion, regardless of the timing of initiation of cooling.

We included literature searches from Ovid Medline 1950–2009, the Cochrane Library, EMBASE 1988–2009, Google scholar and citation tracking. The search sought to identify studies that evaluated the use of MTH following OHCA using the search criteria above. Finally, a Web of Science citation search was performed on all included studies. Reference lists of all available primary studies and review articles were obtained to identify potentially relevant citations. Previously published systematic review articles were sought, looking for particular relevance to using MTH in the prehospital and ED setting. After a generalised search, limits were applied for 'trials'.

Human trials were assessed using the Jadad system[18] to assess internal validity. This allows a measure of comparison of quality between trials.

RESULTS

One thousand and sixty-two papers were screened for inclusion. These were subdivided into animal studies, non-randomised studies, randomised trials and systematic reviews. Two systematic reviews and five randomised clinical trials were identified. Five animal trials comparing timing of cooling initiation were included.

Animal studies

The first animal studies using hypothermia after cardiac arrest were reported in the 1950s. In the early 1960s, Peter Safar observed that dogs that were mildly hypothermic at the initiation of experimental cardiac arrest had a better neurological outcome than dogs that were normothermic.[19]

A summary of selected animal studies is shown in table 1. These particularly relate to early cooling and the potential effect this may have on outcome.

The discovery of the neuroprotective effects of mild to moderate hypothermia led to the investigation of resuscitative hypothermia in several animal models. Dogs treated with immediate mild (34°C) or moderate (30°C) hypothermia showed improved functional and histological outcome. Dogs treated with deep hypothermia (15°C), however, showed no improvement in neurological function and had more severe cerebral histological changes compared with mild or moderate hypothermia groups.[13 23] In the same model, delaying the onset of cooling until 15 min postreperfusion was not associated with the same improvement in functional outcome but did improve histological damage. MTH was not associated with any significant side effects in these studies.

More recently a trend towards better outcomes after earlier initiation of therapeutic hypothermia (<15 min post-ROSC) has been demonstrated.[20 22] Kuboyama and colleagues demonstrated that survival without neurological deficit can still be achieved after 40 min of VF cardiac arrest in dogs when intra-arrest hypothermia is instigated using cold intravascular fluids. However, a delay in cooling after the induction of VF was

Table 1 Animal models of therapeutic hypothermia after out-of-hospital cardiac arrest

Study (year)	Animal model	Cooling method + target temperature	Duration of cooling	Outcome	Comments
Sterz[13]	30 dogs. 10 min VF arrest model. RCT of cooling during CPR vs early post-ROSC cooling vs normothermia	Cooling externally 34°C	20 h	Improved neurological outcome when cooling started during CPR or immediately after ROSC	External CPR and resuscitation drugs used as per human practice
Kuboyama[20]	22 dogs, induced VF for 12.5 min. Prospective RCT of normothermia vs immediate hypothermia vs delayed (15 min after reperfusion) cooling	Cooling on bypass 34°C	1 h	Immediate cooling showed trend towards better functional outcome compared with delayed cooling and associated with lower histological damage scores	Functional outcome did not reach statistical significance
Nozari[21]	27 dogs. VF cardiac arrest model with 40 min no-flow time. RCT of normothermia vs mild hypothermia vs moderate hypothermia	Cooling with venovenous extracorporeal shunt 34°C	12 h	Mild or moderate hypothermia during prolonged CPR improved survival and functional outcome	Invasive techniques used; not easily applicable to humans
Abella[22]	30 mice. Potassium-induced arrest. Prospective RCT of intra-arrest cooling vs delayed (20 min) postarrest cooling vs normothermia	Cooling with cooling blanket 30°C	1 h	Intra-arrest cooling showed better survival to 72 h than delayed cooling or normothermia	Results statistically significant. Only asystolic arrests.
Zhao[12]	45 mice. Potassium-induced cardiac arrest for 8 min. Prospective RCT of normothermia vs intra-arrest cooling vs prolonged resuscitation (9.5 min) to initiate cooling	Cooling with cooling blanket 30°C	90 s	Animals treated with hypothermia, even in prolonged ischaemia group showed improved survival compared with normothermic controls. Haemodynamic variables also improved.	Results statistically significant. Early intra-arrest cooling possible only in prehospital setting. Intra-arrest cooling may be useful for haemodynamic resuscitation

CPR, cardiopulmonary resuscitation; RCT, randomised controlled trial; VF, ventricular fibrillation; ROSC, return of spontaneous circulation.

associated with an increased mortality and poorer neurological outcomes.[20] Nozari showed that early intra-arrest cooling in dogs with 60 min of VF resulted in a favourable neurological outcome.[21] However, when cooling was delayed until 20 min after onset of VF, seven of eight dogs did not survive. Abella and colleagues showed that mice cooled 20 min after cardiac arrest showed a higher mortality than mice cooled just prior to resuscitation from an 8 min period of cardiac arrest.[22] Zhao demonstrated in a randomised, controlled, murine model that delaying resuscitation to institute therapeutic hypothermia still resulted in a favourable neurological outcome.[12]

The animal studies reviewed suggest that cooling should commence with a minimum of delay after cardiac arrest and should continue for at least 24 h to confer lasting neuroprotection.

Non-randomised trials

The first reported human studies using therapeutic hypothermia were reported in 1958.[24] Since then >20 non-randomised studies have been published. The target temperature has consistently been 32–34°C using a variety of cooling techniques. Reported favourable neurological outcome rates vary from 25% to 68%. A summary of non-randomised trials is shown in table 2.

In 1997, Bernard and colleagues conducted a pilot study comparing patients treated with MTH, induced by the application of ice packs, with normothermic controls. They demonstrated improved outcome in the treatment group, without significant complications.[6] Yanagawa cooled 13 patients who had survived initial resuscitation.[7] Cooling to 33°C commenced on arrival at the ED (time to target temperature of 5.5 h post-ROSC) and was maintained for 48 h before slowly rewarming at 1°C per day.

Further studies adopted progressively more sophisticated means of inducing therapeutic hypothermia. A study using cold air surface cooling in the ED by Zeiner and colleagues was successful in lowering core body temperature.[25] Despite non-significant results, these studies supported the evidence that MTH was a safe clinical intervention and could improve outcome after OHCA.

Cooling modalities are summarised in table 3. Methods of initiating prehospital cooling have been investigated, with cold fluids and ice packs being the modalities of choice.[28 29] Other methods of cooling, including body surface cooling with ice and cold blankets, helmet devices, endovascular cooling catheters, haemofiltration and coronary bypass, have been studied. None of these combines efficacy with ease of use. A key finding is that infusion of up to 2 litres of cold (4°C) intravenous fluid (0.9% saline or Ringer's lactate) in the immediate post-ROSC phase is an effective and safe method of cooling and is not associated with significant complications or cardiovascular instability. Whatever the cooling technique employed the degree of hypothermia induced is important, and Merchant and colleagues have demonstrated that overcooling is a significant risk and careful core body temperature monitoring is mandatory.[30] The risks of overcooling include infection, coagulopathy and cardiac arrhythmias.

Randomised trials

Five randomised clinical trials of therapeutic hypothermia post-IHCA have been published.[2 3 32–34] These are summarised in table 4. The first clinical trial of therapeutic hypothermia, published in 2001,[32] enrolled 30 patients following OHCA with asystole or pulseless electrical activity (PEA) as the initial cardiac rhythm. Sixteen patients were cooled to 34°C for a maximum of 4 h with a helmet cooling device and then allowed to rewarm passively. Two of the patients treated with MTH survived with a favourable neurological outcome compared with no patients in the normothermia group.

In 2002, two prospective, RCTs of MTH in the post-resuscitation management of witnessed OHCA were published.[2 3]

Table 2 Non-randomised studies

Study	Year	Initial cardiac rhythm	Cooling method + target temperature	T_{targ} (min)	Duration of cooling	Outcomes
Bernard[6] (n=22)	1997	Any	Ice packs 33°C	74	12 h	No significant side effects. Increased survival and better neurological outcome compared with historical controls
Yanagawa[7] (n=13)	1998	Any	Cooling blanket 33–34°C	414	48 h	Cooling associated with increased rates of pneumonia. Higher survival and recovery rates in hypothermia group
Zeiner[25] (n=27)	2000	Any	Cold air	276	>24 h	No major complications in first 24 h. Mild resuscitative hypothermia shown to be safe and feasible
Felberg[26] (n=9)	2001	Any	Cooling blanket	378	24 h	No major complications. Cooling methods found to be slow and imprecise. Favourable neurological outcome demonstrated
Bernard[27] (n=22)	2003	Any	Cold fluids (30 ml/kg 4°C Ringer's), ice	ASAP		Rapid drop in core body temperature from 35.5 to 33.8°C, improved BP and renal function. No cases of pulmonary oedema
Kim[28] (n=17)	2005	Any	Cold fluids (2 litres of 4°C saline)	ASAP	24 h	Fluid infusion did not alter ejection fraction, central venous pressure or pulmonary pressures
Busch[29] (n=27)	2006	Any	Sports ice packs and water-soaked towels placed prehospital	450	12–24 h	Cooling rates found to be slow. Higher in-hospital survival rates in cooled patients
Merchant[30] (n=32)	2006	Any	Cooling blanket	360	12–24 h	Majority of cases showed unintentional overcooling to <32°C
Kliegel[31] (n=20)	2007	Any	Cold fluids (4°C saline 30 ml/kg/h)	60	24 h	Majority reached <34°C in <60 min

ASAP, as soon as possible; BP, blood pressure; T_{targ}, time to target temperature.

Table 3 Cooling methods

Invasive techniques	Non-invasive techniques
Cold intravenous fluid infusion	Ice packs
Extracorporeal cooling blood circuit	Cooling blankets (water/air filled)
Cardiopulmonary bypass	Cooling helmets (water/air filled)
Femoral–carotid bypass	Cold water immersion
Lavage	Self-adhesive cooling pads
Nasal/nasogastric/rectal/peritoneal	
Ice slush	
Endovascular cooling catheter	

Both of these studies recruited a highly selective cohort of patients, with 92% of patients initially assessed for eligibility excluded.

Recruitment criteria for both trials were similar and included ROSC in patients who remained intubated and ventilated after OHCA due to VF of presumed cardiac aetiology.

The European trial cooled 136 patients to a core temperature of 32–34°C using a mattress cover that delivered cold air. The aim was to reach target temperature within 4 h of ROSC, maintain it for 24 h and then allow passive rewarming to occur. The study showed the number needed to treat (NNT)=6 (RR 1.40, 95% CI 1.08 to 1.81) for a favourable neurological outcome when MTH was used. The overall mortality at 6 months was reduced from 55% in the normothermia group to 41% in the MTH group, NNT=7 (RR 40.74, 95% CI 0.58 to 0.95).

In the Australian study cooling was initiated prehospital by applying ice packs to the head and torso. The target temperature (33°C) was maintained for 12 h posthospital admission before patients were actively rewarmed after 18 h. Forty-three patients were cooled; 21 (49%) had a favourable neurological outcome of living at home or within a rehabilitation facility (RR 1.85, 95% CI 0.97 to 3.49, NNT=4). Mortality was reduced from 68% to 51% in the hypothermia group (RR 0.76, 95% CI 0.52 to 1.10, NNT=6). These findings led to the European Resuscitation Council, in association with the International Liaison Committee on Resuscitation and the American Heart Association, recommending MTH as standard treatment for OHCA victims that achieve ROSC following a VF arrest.[8]

A randomised trial[33] of inducing MTH by isovolumic haemofiltration in patients after OHCA showed an increased survival benefit, but it was unclear whether this was conferred by the hypothermic or filtration processes. This technique is not suitable for use in the emergency and prehospital environment.

A recent clinical pilot study explored the benefit of cooling patients immediately after OHCA using intravenous cold saline administered by paramedics in the field.[34] An infusion of 500–2000 ml of 0.9% saline at 4°C was administered. Subsequent in-hospital cooling was at the discretion of the attending physician. Sixty-three patients were treated with prehospital hypothermia. Only 78% of patients in the hypothermia group received further cooling. Prehospital cooling led to a significantly lower temperature on arrival at hospital (34.7°C vs 35.7°C, p<0.0001). There was no significant difference in survival to hospital discharge in the hypothermia versus normothermia groups (33% vs 29%, p=0.70). Subgroup analysis of patients with VF as the initial cardiac rhythm showed a trend towards increased survival to hospital discharge but there was a trend towards increased mortality in the cooling group where the initial cardiac rhythm was PEA or asystole.

Table 4 Randomised clinical trials

Study (no. of patients)	Initial Year cardiac rhythm	Cooling method + target temperature	T_{targ}	Duration of cooling	Patients	Survival to hospital discharge	Favourable neurological outcome	Jadad	Comments
Hachimi-Idrissi[32] (n=30)	2001 Asystole or PEA	Cooling helmet 34°C	3 h post-ROSC	4 h	16 MTH 14 normothermia	MTH: 2/16 (13%) Normothermia: 0/14	Same as survival rate	3	Results NS (p=0.49)
Bernard[2] (n=77)	2002 VF or pulseless VT	Ice packs 33°C	2 h post-ROSC	12 h	43 MTH 34 normothermia	MTH: 21/43 (49%) Normothermia: 9/34 (26%)	Same as survival rate. OR for favourable neuro. recovery 5.25 (95% CI 1.47 to 18.79)	1	Results significant (p=0.046)
HACA[3] (n=275)	2002 VF or pulseless VT	Cooling mattress/ice packs 32–34°C	6 h after initiating cooling	24 h	136 MTH 137 normothermia		MTH: 75/1236 (55%) NT: 54/137 (39%)	3	Trend towards high infection rate in hypothermia group but benefit deemed to outweigh risk
Laurent[33] (n=61)	2005 VF or asystole	Cooling of the substitution fluid on haemofiltraiton		24 h	20 Haemofiltration 22 Haemofiltration + hypothermia	OR for survival 4.4 (95% CI 1.1 to 16.6)		2	Results from haemofiltration alone were similar to haemofiltration with MTH. Haemofiltration is not practical for use within ED
Kim[34] (n=125)	2007 All rhythms after non-traumatic OHCA	Infusion of up to 2 litres of 4°C saline prehospital	Variable	Variable	63 cooling 62 normothermia	NS		3	Significantly lower ED arrival temperature (34.7 vs 35.7°C) in group treated with cold intravenous fluid. Trend towards worse survival in non-VF patients treated with hypothermia. Only 78% randomised to cooling received treatment

ED, Emergency Department; MTH, mild therpautic hypothermia; NS, non-significant; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; T_{targ}, time to target temperature; VF, ventricular fibrillation; VT, ventricular tachycardia.

Systematic reviews

Two systematic reviews matched our inclusion criteria. Cheung *et al* reviewed the combined data from four RCTs in 2006,

representing 436 patients.[17] Inclusion criteria were adults with primary OHCA who remained comatose after ROSC. The clinical trials ranged from score 1 to 3 on the Jadad scale and A–C on the Cochrane grade score. The combined data showed that MTH decreased in-hospital mortality (RR 0.75, 95% CI 0.62 to 0.84). The review concluded that MTH had an NNT of 5 to improve neurological outcome and an NNT of 7 to save a life. However, the review failed to draw conclusions on the optimum cooling method, rate or duration of cooling. No evidence of treatment-limiting side effects was reported.

A meta-analysis[16] of three trials has shown that patients treated with hypothermia show an increased rate of survival with favourable neurological outcome (RR 1.68, 95% CI 1.29 to 2.07). The calculated 95% CI for the NNT to result in a patient being discharged from hospital with a favourable neurological outcome ranged from 4 to 13.

DISCUSSION

There is strong evidence to support the use of MTH in comatose patients after OHCA whose initial cardiac rhythm was VF. The evidence supporting MTH use in other presenting cardiac rhythms is less clear and further studies are required. Despite animal studies demonstrating the benefit of immediate cooling, either during cardiopulmonary resuscitation (CPR) or immediately post-ROSC,[12 20 22] the existing evidence from human studies is less clear.[14] Practically, initiating cooling in the prehospital environment is challenging; however, several studies have shown that initiating cooling in the ED is feasible and effective.[27 28 31] The different cooling modalities are shown in table 3. The use of ice packs is a simple, but relatively slow, means of cooling. A bolus of cold intravenous fluids combines efficacy with ease of use and is not associated with significant unwanted side effects. This is probably the cooling method of choice for the ED. Intravenous fluids can be stored in a refrigerator within the ED and administered to patients following OHCA shortly after arrival in hospital. Initiating cooling in the ED is likely to shorten the time to target temperature, particularly if the patient requires coronary intervention or radiological imaging prior to ICU admission. Cooling with cold intravenous fluids can continue during transfer or during clinical procedures.

The three phases of therapeutic hypothermia are induction, maintenance and rewarming. For all phases, accurate core body temperature measurement is essential to ensure accurate cooling and prevent overcooling. For rapid induction, oesophageal or central venous temperature should be measured, as probes in the bladder or rectum do not reflect core body temperature accurately.[35] Overcooling is common.[30] After induction, therapeutic hypothermia can be maintained on the ICU with body surface cooling techniques with accurate feedback mechanisms, or invasive, endovascular cooling techniques. In order to prevent shivering, paralysis and sedation are required. The optimum length of time for which MTH should be maintained remains unknown,[11 36] but previous studies have used maintenance periods of 12–48 h.[2 3] The optimum means, whether active or passive, and rate of warming are unknown, and further research is required to improve the induction, maintenance and rewarming phases.

Despite strong evidence suggesting benefit, uptake of therapeutic hypothermia in routine clinical practice has been slow.[10 37] Lack of awareness, fear of a novel treatment and unknown side effects, as well as lack of equipment, have been cited as barriers to MTH implementation.[38]

CONCLUSION

The use of MTH in patients who remain comatose after OHCA improves survival and neurological outcome. The optimal time of initiation, cooling method and target temperature have yet to be established. Cooling is feasible within the ED, and cold intravenous crystalloid infusion is effective, simple and safe. Wider awareness among ED medical staff may increase the early use of therapeutic hypothermia in patients after OHCA.

Competing interests None.

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Issues around conducting prehospital research on out-of-hospital cardiac arrest: lessons from the TOPCAT study

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ABSTRACT

Outcome from OHCA is primarily determined by prehospital events and meaningful clinical OHCA research must include data recorded in this setting. There is little evidence on which to base the practice of prehospital resuscitation and research in this area presents huge challenges but is required if survival from OHCA is to improve. This short report aims to provide a practical guide to performing prehospital research on OHCA, based on lessons learned from the Temperature Post Cardiac Arrest (TOPCAT) research; an observational study into OHCA.

BACKGROUND

Out-of-hospital cardiac arrest (OHCA) remains one of the leading causes of mortality across Europe.[1] In the 1970s academic clinicians brought out-of-hospital cardiac arrest (OHCA) research into the prehospital arena, dramatically improving survival.[2 3] Recent publications have highlighted the requirement for out-of-hospital clinical research if basic science is to translate into clinical benefit.[4] This report presents a practical description of some of the challenges involved in United Kingdom prehospital research based on experiences with the Scottish Temperature Post Cardiac Arrest (TOPCAT) study.

In brief, TOPCAT is a prospective observational study of patients with OHCA during the prehospital phase of resuscitation, while in the Emergency Department, and through to the Intensive Care Unit. Measurements include core body temperature and serum markers of systemic inflammation and brain injury. So far, 137 patients have been enrolled from OHCA resuscitation events involving approximately 160 different ambulance service personnel (see Table 1).

PLANNING A PREHOSPITAL STUDY

Ethical approval and consent

The ethical considerations relating to prehospital research are challenging.[5] Patients in cardiac arrest are unconscious, and in Scotland, the Adults with Incapacity Act strictly governs research involving these individuals. Ethical approval from a national Research Ethics Committee (REC) is required before undertaking research involving this patient group. For the TOPCAT study the REC agreed that consent should be sought from the participant's next-of-kin at the earliest opportunity. Should the patient recover sufficiently, retrospective, informed consent is sought from them. This approach of waiving initial consent is being more widely adopted to facilitate research involving incapacitated adults in an emergency setting.[6]

Coordinating across agencies

For prehospital research to be successful, cooperation between members of the research team, Emergency Medical Dispatch Centre (EMDC), Emergency Medical Services (EMS) personnel, Emergency Department and Intensive Care Unit is vital. All EMS personnel likely to be involved in the study need to be informed and aware of the research protocol.[5 7] Although EMS personnel may not be responsible for data collection on-scene, interaction between all members of the clinical and research team ensures optimum patient care and data collection.

Collecting prehospital data

Prehospital research requires excellent relations with the local ambulance service. EMS in the United Kingdom do not routinely task a prehospital doctor to OHCA but in the present study, an Emergency Medicine Specialty Registrar performs the field research. In order to gather data it may be necessary to perform clinical interventions not routinely carried out by EMS such as oesophageal temperature probe insertion or jugular vein cannulation to obtain enough blood for subsequent analysis. Blood samples are promptly transported back to the hospital, being kept cool with disposable chemical cooling packs.

Dispatch

In order to allow EMDC to track the registrar's location and availability to respond the TOPCAT research, the registrar's car is fitted with a compatible satellite transponder. On receipt of a possible cardiac arrest call, EMDC first dispatches an ambulance response then contacts the research registrar on a mobile phone, which is switched on only during on-call periods. A marked response car equipped with audible and visual warning systems is used, which has the authorisation of the local police.

Training, insurance and liability

The research registrar received formal response driver training from the Scottish Ambulance Service but such training is available from the police or commercial sources. A specific insurance policy is required to cover emergency driving. This is available through several motor insurance brokers adding approximately 10% to the regular car insurance policy (eg, Towergate MIA, London).

Table 1 Summary of prehospital activity for the temperature post cardiac arrest (TOPCAT) study (1/08/08–1/10/09)

Total Emergency Medical Dispatch Centre calls to TOPCAT to date	137
Calls attended	106
Cardiac arrest with attempted resuscitation	55
Mean response time ambulance	7.4 min
Mean research doctor response time	10.4 min

On-scene data recorded by the EMS crew and research doctor are correlated with electronic data from EMDC. Ambulance and doctor response, together with on-scene times are automatically recorded via the tracking systems, which update every 13 s.

On arrival at the scene, the research registrar may be requested to assist the attending EMS crew. Clinical care of the patient always remains a priority and data collection only commences when life-saving interventions have been performed. Although no additional medical equipment is carried by the research registrar, he frequently assists with endotracheal intubation, intravenous cannulation and provides reassurance and encouragement.

Only through novel, prehospital research studies involving close collaboration between clinical researchers and frontline EMS crews is outcome from OHCA likely to be improved.

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Ethics approval This study was conducted with the approval of the Scottish Research Ethics Committee.

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Early in-hospital management of out-of-hospital cardiac arrest in Scotland: a national survey

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Guidelines recommend the use of mild therapeutic hypothermia (MTH) and percutaneous coronary intervention (PCI) in the early post-resuscitation management of select out-of-hospital cardiac arrest (OHCA) cases. This study aims to assess the current use of MTH and PCI in Scottish Emergency Departments (ED) and Intensive Care Units (ICU). We conducted a questionnaire survey of all the Scottish Emergency Medicine Consultants, EDs and ICUs. MTH was more commonly initiated in ICU than in the ED (19; 91 vs. 7; 37%, $P<0.05$). Only a minority two (11%) EDs routinely referred OHCA patients for early PCI and only three (16%) EDs receiving patients after OHCA had on-site access to PCI facilities. The use of MTH after OHCA appears to be widespread, although it is infrequently initiated in the ED. The utilization of PCI in OHCA management has yet to be widely established. Increased awareness may increase the use of promising therapies such as MTH and PCI following OHCA to save lives. *European Journal of Emergency Medicine* **18:102–104 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Coronary heart disease is responsible for around 110 000 deaths in the UK every year with 75% because of sudden cardiac death [1]. In Scotland, there are over 3500 out-of-hospital cardiac arrests (OHCA) annually, with survival to hospital discharge less than 5% [2].

In the pre-hospital phase effective resuscitation is required to obtain the return of spontaneous circulation (ROSC). The only therapy in the post-ROSC phase of OHCA shown to improve outcome is mild therapeutic hypothermia (MTH) [3,4]. This study surveys the use of MTH in Emergency Departments (ED) and Intensive Care Units (ICU) across Scotland.

In 2002, two prospective, randomized controlled trials of MTH in the post-resuscitation management of witnessed OHCA were published [3,4]. These papers led to the European Resuscitation Council and the International Liaison Committee on Resuscitation recommending MTH as standard therapy for OHCA patients with ventricular fibrillation as the presenting rhythm who remain comatose post-ROSC [5]. Whether MTH may also benefit patients after OHCA with non-ventricular fibrillation presenting rhythms is unknown.

There is still uncertainty amongst physicians about using MTH [6]. Recent evidence suggests that early achievement of the desired hypothermic temperature is associated with a better neurological outcome. If target temperature is to be achieved early, cooling will need to commence in the pre-hospital or ED phase of the OHCA patient's care. Primary percutaneous coronary intervention (PCI) can be considered after ROSC in the management of OHCA. PCI is currently regarded as the most effective reperfusion strategy in ST-elevation myocardial infarction (STEMI) [7]. Whether PCI is beneficial in cases of non-STEMI acute coronary syndrome complicated by cardiac arrest remains under investigation [8].

We sought to investigate the differences in ED and ICU management of OHCA patients in Scotland and to establish the degree of consistency in the use of MTH and PCI in the management of OHCA. We sought to establish possible reasons for variation in clinical practice and barriers to implementation.

Methods

A national questionnaire survey was conducted of all emergency medicine (EM) consultants, EDs and ICUs in Scotland. Each consultant was e-mailed with an invitation to complete a web-based questionnaire. All responses were anonymous and participation was voluntary.

A telephone survey was conducted of all Scottish EDs ($n = 26$) and Intensive Care Units ($n = 22$). On receipt of the telephone call, a member of the on-duty medical team was asked to answer the survey questions. Ethical approval was gained from the University of Edinburgh Student Projects Committee.

Results

One hundred and thirteen EM consultants were identified as working in Scotland. Contact e-mail addresses

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were available for 87 of these consultants. Thirty-two (37%) of the contacted EM consultants completed the survey. All 26 Scottish EDs and 22 Intensive Care Units were contacted by telephone. The telephone survey was completed by 19 (73%) EDs and 21 (96%) ICUs.

Emergency medicine consultant views on OHCA management

Thirty-two EM consultants responded to the survey. The majority (27; 84%) felt MTH was effective in the management of OHCA patients and 26 (84%) had experience of using MTH. A large proportion, (29; 91%) of EM consultants thought MTH should be commenced earlier (pre-hospital or ED setting). Twenty-nine (91%) EM consultants thought it practical to initiate MTH within the ED.

Twenty-one (67%) of ED consultants did not think PCI should be used routinely in the early management of OHCA. The major trigger for PCI referral was reported as an ECG finding of ST-segment elevation.

Emergency Department management of OHCA

Seven (47%) EDs had used cooling before, compared to 19 (91%) ICUs. MTH was more commonly initiated in ICU than in the ED. [19 (91%) vs. seven (37%), $P < 0.05$]. The majority of EDs (nine; 47%) did not routinely initiate cooling. A protocol for MTH was only present in four (21%) EDs, as shown in Table 1.

A protocol for primary PCI use following OHCA was available in 10 (53%) EDs. None of the district general hospitals that received patients following OHCA had on-site access to PCI. Fifty-nine percent of university teaching hospitals had on-site access to PCI.

Table 1 Emergency Department management of OHCA ($n=19$)

Ever used MTH in the ED on a patient post-OHCA?	
Yes	7 (37%)
No	12 (63%)
Is it practical to initiate MTH within the ED?	
Yes	15 (79%)
No	4 (21%)
Proportion of post-OHCA patients who have MTH initiated in the ED	
None	14 (74%)
<10%	3 (16%)
10–25%	1 (5%)
>25%	1 (5%)
ED protocol for MTH use in OHCA patients	
Yes	4 (21%)
No	15 (79%)
Method of initiating MTH (if used)	
Ice packs	4 (21%)
Surface cooling blankets	2 (11%)
Exposure only	1 (5%)
Cold IV fluids	0 (0%)
Reasons for not initiating MTH in ED	
MTH commenced on ICU	8 (42%)
Cooling equipment unavailable	6 (32%)
Insufficient evidence for using cooling	5 (26%)
Protocol in place for PCI following OHCA	
Yes	10 (53%)
No	9 (47%)
What proportion of post-OHCA patients go for PCI from the ED?	
None	4 (21%)
<10%	11 (58%)
10–25%	2 (11%)
>25%	0 (0%)
Access to PCI facility from the ED	
On-site	3 (16%)
Off-site	14 (74%)
No	2 (10%)
Availability of PCI facilities	
24 h a day	11 (58%)
Monday–Friday 09:00–17:00	5 (26%)
Available on request	3 (16%)

ED, Emergency Department; ICU, Intensive Care Unit; MTH, mild therapeutic hypothermia; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention.

Intensive Care Unit management of OHCA

The majority of ICUs (19; 91%) had experience of cooling OHCA patients and utilized a protocol (16; 76%), as shown in Table 2. The majority of OHCA patients admitted to ICU were cooled with MTH being used in over 50% of admitted OHCA patients in 14 (67%) ICUs.

Discussion

This study reports on a national survey of Scottish EDs, ICUs and EM consultants. Compared to studies published earlier, we have found an increase in the use of MTH in both the ED and ICU setting. A UK survey in 2006 of 98% of all British ICUs found that only 27% had ever used MTH [9]. Our study reports a 90% MTH experience rate which may imply an increase in the use of MTH on the ICU for post-OHCA patients. We found the majority of Scottish ICUs have adopted a cooling protocol but there remains a variation in the cooling techniques used and in the length of time MTH is maintained, perhaps reflecting the lack of clinical evidence in these areas.

The consensus from clinical studies supporting early cooling has led the International Liaison Committee on Resuscitation to recommend the initiation of MTH as soon as possible after ROSC [10]. If target temperature is

Table 2 Intensive Care Unit management of OHCA ($n=21$)

Ever used MTH in the ICU on a patient post-OHCA?	
Yes	19 (90%)
No	2 (10%)
Proportion of post-OHCA patients who have MTH initiated in the ICU	
None	2 (10%)
<10%	0 (0%)
10–25%	2 (10%)
>25%	17 (80%)
ICU protocol for MTH use in OHCA patients	
Yes	17 (81%)
No	4 (19%)
Method of initiating MTH (if used)	
Ice packs	13 (62%)
Surface cooling blankets	14 (67%)
Cold IV fluids	8 (38%)
Wet towels and fanning	5 (24%)
Invasive cooling	2 (10%)
How long are patients cooled on ICU for? (if applicable)	
<6 h	0 (0%)
6–12 h	1 (5%)
12–24 h	2 (10%)
24–48 h	15 (71%)
>48 h	1 (5%)

ICU, Intensive Care Unit; MTH, mild therapeutic hypothermia; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention.

to be achieved early, cooling will almost certainly have to be initiated in the pre-hospital or ED phase of an OHCA patient's care. Ninety-one percent of EM consultants thought it practical to initiate MTH in the ED. There appears to be a positive attitude towards MTH but our study has shown a discrepancy in best perceived clinical practice and actual delivered treatment.

None of the surveyed university teaching hospitals routinely used MTH in the ED. The barriers to implementation most often cited for non-use of MTH were lack of a cooling protocol, lack of cooling equipment or MTH being initiated in the ICU instead. Studies have earlier reported similar reasons to our non-adoption of MTH with the most commonly cited reasons being: lack of evidence, lack of a protocol, difficulties in practicality and lack of resources [6]. Establishing protocols for MTH use in the ED and heightened awareness could promote the use of cooling in the early OHCA management.

Early post-ROSC PCI has also been shown to improve the survival when used in patients surviving OHCA. Evidence suggests OHCA STEMI patients are likely to benefit from early PCI [8]. Whether non-STEMI post-OHCA should have PCI remains unknown and further research is warranted to ensure that the intervention occurs in the correct subset of post-OHCA patients. The management of OHCA needs to be coordinated on a regional scale in the form of a cardiac network to ensure patients requiring reperfusion intervention are transported to the appropriate centre. In our study, none of the district general hospitals receiving OHCA patients had on-site access to primary PCI. Some hospitals transferred OHCA patients direct for PCI. The early use of PCI has yet to be widely accepted and physicians are still unsure of its place in the management of OHCA.

There are several limitations to this study. Our low-sample size may not reflect the opinions and practice of all physicians in Scotland involved in the care of OHCA patients. The telephone survey only interrogated one respondent per department and there is no way of confirming the answers being provided.

Conclusion

We have shown that the use of MTH in Scottish EDs is low. Use of MTH on ICU is increasing. Few EDs routinely refer OHCA patients for primary PCI and a concerning number of hospitals receiving patients post-OHCA do not have on-site access to primary PCI facilities. Greater understanding of the role of MTH and PCI in the early management of OHCA will promote these promising treatments amongst emergency and critical care physicians.

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Improving survival from out-of-hospital cardiac arrest

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Abstract

Out-of-hospital cardiac arrest (OHCA) is a leading cause of prehospital mortality and serious neurological morbidity. Survival from OHCA almost entirely depends on prehospital intervention by ambulance personnel. Recent evidence has shown the importance of good quality cardio-pulmonary resuscitation (CPR) in improving outcome from OHCA. Recent studies have suggested that intubation, intravenous cannulation and drug administration may distract from basic CPR and be associated with poor outcomes following OHCA. This article reviews the latest evidence on prehospital OHCA management and presents the case for a 'back to basics' approach.

Key words
● Cardiac arrest ● Defibrillation ● Prehospital care ● Resuscitation

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Out-of-hospital cardiac arrest (OHCA) is a major cause of mortality and morbidity in the UK and presents the commonest immediate life-threatening medical emergency ambulance crews face (Cobb et al, 1996). Survival from OHCA is almost entirely dependent on the prehospital resuscitation attempt, but overall survival to discharge remains poor (<10%). Out-of-hospital cardiac arrest presents unique challenges for ambulance personnel and survival is almost entirely dependent on the prehospital interventions performed.

The challenge of cardiac arrest

Rapid access to the scene is critical and ambulance response time targets are largely based on OHCA research. At-scene, a number of complex tasks need to be undertaken, often with a limited amount of space, poor lighting or distressed bystanders. The initial actions of the on-scene ambulance crew will often determine whether the OHCA patient survives. Extrication of OHCA patients can be challenging—continuing effective resuscitation while carrying a patient on a stretcher is almost impossible and performing chest compressions in a moving ambulance poses significant risks to the ambulance crew.

In recent years, resuscitation research has highlighted the need to focus on the fundamentals of resuscitation, namely CPR and defibrillation, and has brought into question advanced airway management and resuscitation drug administration.

Improving cardiac arrest survival

This year marks the 50th anniversary of modern cardio-pulmonary resuscitation (Kouwenhoven et al, 1960). The 'chain of survival' still remains vital for a successful resuscitation outcome, with early access, early CPR, prompt defibrillation and early advanced care, including therapeutic hypothermia, being key for survival.

The only three therapeutic interventions proven to improve survival from OHCA are good quality CPR, prompt defibrillation and therapeutic hypothermia. Modern paramedics are taught advanced airway skills, intravenous cannulation and can administer a range of intravenous drugs. However, with an increasing number of paramedics, skills atrophy is a risk and even paramedics operating in densely populated regions are only likely to encounter a small number of OHCA per year.

Most ambulance services measure return of spontaneous circulation (ROSC) as a key performance indicator, but recent studies have shown that ROSC is not necessarily associated with survival to hospital to discharge, which is the meaningful clinical outcome measure for OHCA (Olasveengen et al, 2009a). Ambulance services striving to improve survival from OHCA need to measure survival to hospital discharge in addition to ROSC rates.

Cardiac compressions and defibrillation

Cardiopulmonary resuscitation is vital to maintain cerebral and cardiac perfusion until ROSC can be achieved. Studies suggest that immediate bystander CPR doubles the chances of survival

to discharge compared to delaying CPR until emergency medical assistance arrives (Gallagher et al, 1995). The quality of CPR delivered by ambulance personnel is vital. Studies have reported the adverse physiological consequences of poor resuscitation technique and have demonstrated that quality of CPR influences the outcome from OHCA (Frenneaux, 2003).

Chest compressions aim to provide adequate perfusion to the vital organs, including the heart, during cardiac arrest. A short period of just a few seconds off the chest leads to intra-cardiac pressure changes—the right ventricle dilates and the left ventricle is compressed, leading to a cardiac state where even in the presence of ventricular fibrillation, a defibrillatory shock will not be effective.

Tracheal intubation, establishing intravenous access and extrication all interrupt chest compressions. Neither endotracheal intubation nor administration of resuscitation drugs have been definitively shown to improve survival from OHCA (Olasveengen et al, 2007). Recent evidence suggests an increased 'hands off chest' during CPR is associated with poor outcome (Christenson et al, 2009).

Cardiac rhythm recognition can be performed by trained healthcare professionals, including many ambulance crews, or automated cardiac rhythm recognition can be used. Automated rhythm analysis will often take longer than an experienced health professional, resulting in increased delay-to-shock times and decreased chance of successful defibrillation (Yu et al, 2002; Kramer-Johansen et al, 2007).

There is a need to monitor compliance of CPR performed by ambulance crews in accordance with current international resuscitation guidelines (Olasveengen et al, 2007) as previous studies have demonstrated poor compliance with recommended chest compression depth, rate and pauses in chest compressions (Wik et al, 2005; Steen and Kramer-Johansen, 2008). There have been calls for regular monitoring of CPR quality and for uniform reporting of CPR variables (Kramer-Johansen et al, 2007a). Determining the quality of prehospital resuscitation performed by ambulance crews in the field is technically difficult, but crucial if prehospital care of OHCA patients is to improve (Olasveengen et al, 2009b).

Currently, there is research ongoing in Scotland evaluating the role of resuscitation downloads and paramedic feedback in auditing prehospital resuscitation quality and assessing whether survival can be improved using trans-thoracic impedance analysis technology, as shown in the Appendix.

Resuscitation drugs

Advanced life support practice has recommended the use of adrenaline, atropine and amiodarone, despite only animal studies suggesting survival benefit. For decades, ambulance personnel have been administering drugs without this practice being critically evaluated in a randomized trial. A group from Oslo in Norway recently undertook such a trial (Olasveengen, 2009a). Despite the challenges of conducting prehospital research, over 900 patients with OHCA were included in the trial. Patients were randomized to standard resuscitation care (including intubation, defibrillation and intravenous drugs) or a protocol that omitted the use of drugs. The study found no significant difference in survival to hospital discharge between the two groups (10.5% in standard care *vs* 9.2% in the no drugs group, p=0.61). There was no difference in the quality of CPR between the two groups. These results question the value of administering drugs during resuscitation from sudden cardiac arrest.

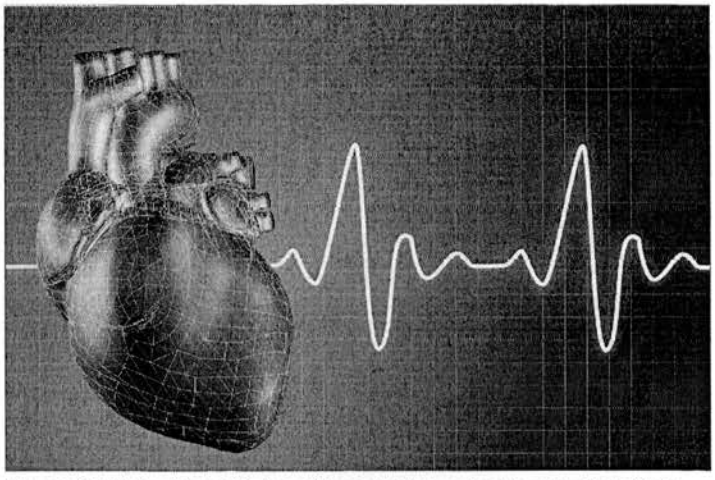

Figure 1. Out-of-hospital cardiac arrest survival is almost entirely dependent on the prehospital interventions performed.

Airway and ventilation

The introduction of paramedic practice by ambulance services aimed to bring advanced life support to the patient including tracheal intubation. Paramedic intubation in the UK is usually limited to patients who do not require drug assisted intubation—the majority of these have had an OHCA.

The most appropriate advanced airway intervention in OHCA is unknown. Tracheal intubation without anaesthetic drugs for OHCA is not associated with increased survival rates (Murray et al, 2002), yet tracheal intubation is currently a core skill on the paramedic syllabus.

There is a significant complication rate associated with prehospital tracheal intubation by

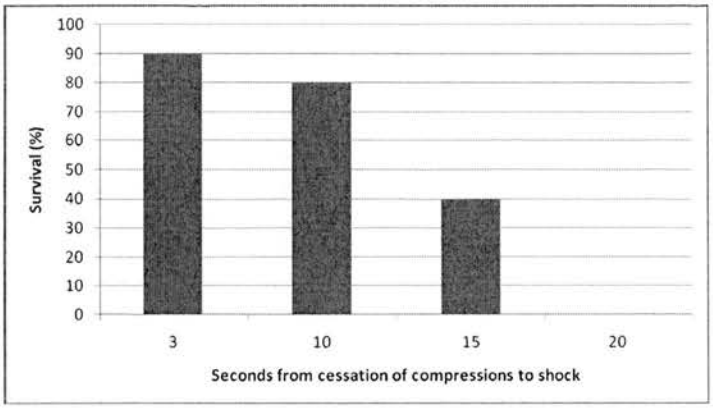

Figure 2. Animal model (murine) showing the effect of increasing the time interval from cessation of chest compressions to delivering a defibrillator shock. In this model, when the 'hands off' time was 20 seconds or greater, no animals survived (Redrawn from: Wu et al, 2002).

Box 1. Improving resuscitation practice

- Resuscitation training, including practical training, is required at least every six months
- Survival to hospital discharge rates should be reported in addition to return of spontaneous circulation following OHCA
- The quality of prehospital resuscitation should be audited in addition to ambulance response time.

paramedics and other airway strategies have been suggested. Supraglottic airway devices are well established in anaesthetic practice and have been used successfully in OHCA patients (Sasada and Gabbott, 1994). Supraglottic airways have recently been recommended by the Joint Royal College Ambulance Liaison Committee (JRCALC).

A recent study from southeast Scotland demonstrated surveyed prehospital tracheal intubation in 628 patients (Lyon et al, 2010). Successful endotracheal intubation was achieved in three or fewer attempts in 573 (91.2%) of these patients. In 55 patients, tracheal intubation was associated with a significant problem, mainly unrecognized oesophageal intubation.

One hundred and ten of 628 patients who underwent prehospital tracheal intubation survived to hospital admission from the ED. 55 patients who did not undergo prehospital tracheal intubation survived to hospital admission. Survival to admission was higher in patients who did not have prehospital intubation performed (33.1 *vs* 17.5%, $p<0.0001$). The LMA was not used on any patients.

Repeated attempts at laryngoscopy or inability to intubate the trachea compromises oxygenation and ventilation, extends on-scene times and increases the risk of aspiration. Advanced airway skills used by paramedics confer no increased survival compared to patients attended by ambulance technicians with basic airway skills (Guly et al, 1995).

Most clinicians rely on a combination of direct vision and auscultation to confirm tracheal tube position. Capnography is the most reliable method of confirming tracheal tube placement in the prehospital setting, but requires a specific electronic monitor. A number of simple devices are available to confirm tracheal placement including the Ambucheck™ device and colorimetry. Many UK ambulances are not equipped with any such device. In patients in cardiac arrest, the delivery of carbon dioxide in the pulmonary circulation can be variable. Capnography can therefore be unreliable in confirming tube position in these patients and should therefore be used in conjunction with other confirmatory techniques.

In this study, prehospital tracheal intubation was associated with decreased rates of survival to admission. The reasons for this are likely to be multi-factorial. Tracheal intubation may distract from providing good quality basic life support, defibrillation and delay on scene times. Tracheal intubation and ventilation with oxygen will result in an inspired oxygen concentration of close to 100%. Ventilating cardiac arrest patients with 100% oxygen may increase oxidative stress and reactive oxygen species production which can contribute to neuronal cell death (Kramer-Johansen et al, 2007a).

A number of studies have examined the use of the laryngeal mask airway (LMA) in OHCA (Olasveengen et al, 2007; Steen and Kramer-Johansen, 2008). The LMA has a number of potential benefits—the need for relatively little training or ongoing competency requirements, ease of insertion and less risk of incorrect placement. Using an LMA in OHCA has few complications and has not been shown to negatively impact on survival when compared to basic airway management (Steen and Kramer-Johansen, 2008).

The 2008 JRCALC guidelines include a recommendation that the use of supraglottic airway devices should be considered by ambulance crews. Currently, however, there is little guidance for paramedics on when to use an LMA or intubate the patient and availability of LMAs varies across UK ambulance services.

A study from Arizona has shown that by delaying intubation and focusing on early continuous chest compressions and defibrillation, survival to discharge after sudden cardiac arrest tripled19 and this finding has been replicated by other emergency medical services (Garza et al, 2009).

Ambulance service resuscitation training

Ambulance paramedic training teaches advanced skills, including advanced airway management, cannulation and drug administration. These newly acquired skills, when eagerly put into practice for the first time, can distract from the basic elements of CPR. While advanced clinical intervention may be required in some cases, accurate clinical decision-making is required to ensure interventions are performed appropriately and paramedic training should address this. For example, the decision on when to move a patient from the OHCA scene, particularly if the patient has a shockable cardiac rhythm, can have far-reaching consequences as CPR on the move is invariably ineffective.

On completion of paramedic certification, there can be minimal on-going training and regular assessment of resuscitation skills. Research has shown that skill decay is present in even the most experienced paramedics and practical training, theoretical updates and assessment should be performed at least every six months (Perkins and Mancini, 2009).

Therapeutic hypothermia

Cooling patients to 32–34°C for 24-hours after a witnessed VF OHCA has been shown to dramatically improve survival (Bernard et al, 2002; The Hypothermia After Cardiac Arrest Study Group, 2002) and has been recommended as standard treatment in the management of these patients. However, a key question on when to commence therapeutic hypothermia remains unanswered—when to start cooling. Previous studies have shown the beneficial effect of therapeutic hypothermia persists even when cooling is commenced several hours after the OHCA (The Hypothermia after Cardiac Arrest Study Group, 2002).

Cooling post-OHCA patients in the prehospital phase requires additional equipment and to-date, no studies have demonstrated that early cooling, in the prehospital phase by ambulance personnel, confers additional survival benefit (Kim et al, 2009; Bernard et al, 2010). Ambulance personnel should, therefore, concentrate on good quality basic resuscitation to achieve ROSC at-scene and ensure a rapid subsequent transfer to hospital, where cooling can commence.

Conclusion

The latest evidence from resuscitation research suggests a 'back to basics' approach is required with a focus on high quality CPR and prompt defibrillation. There is no evidence to support early intubation during resuscitation following OHCA and recent studies question the value of intravenous drug administration during OHCA. Good quality basic prehospital resuscitation, with an emphasis on 'hands on the chest', will save lives.

Key points

- Chest compression fraction is associated with outcome from out-of-hospital cardiac arrest (OHCA).
- Resuscitation should maintain a high 'hands-on-the-chest' time with minimal interruptions for defibrillation.
- Early intubation may be associated with a worse outcome from OHCA.
- Trial data suggest resuscitation drugs do not improve the survival to discharge rate from OHCA.

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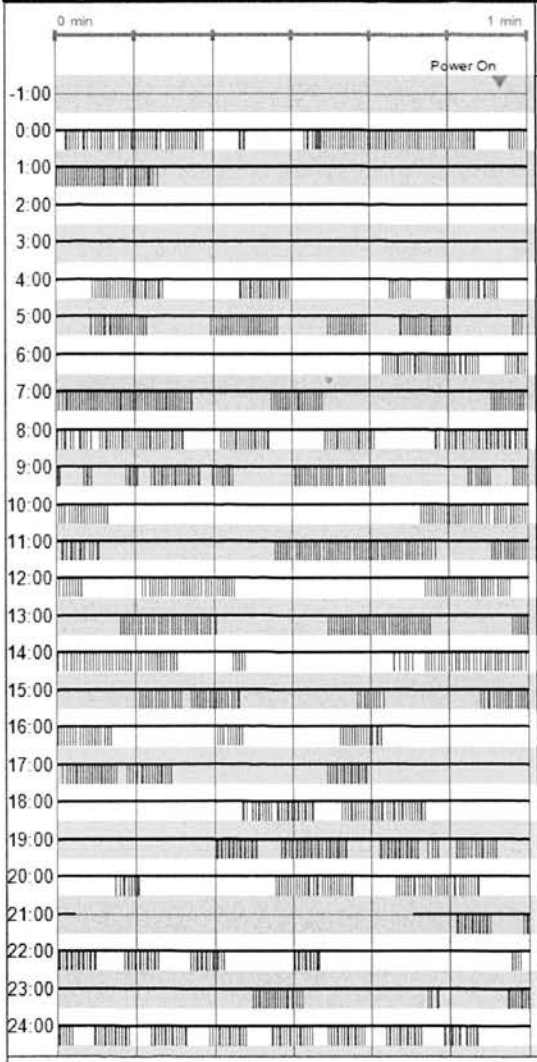
Appendix 1. A download trace from a LIFEPAK 12 defibrillator, analysed using CODESTAT software (Physio Control)



CPR Ratio, %	Prompt. CPR Ratio, %	Compr. Ratio, %	Prompt. Compr. Ratio, %	Compr. Rate	Compr. /min	Vent. Rate	Vent. /min
--	--	--	--	--	--	--	--
98	--	75	--	167	122	--	--
23	--	23	--	166	36	--	--
--	--	--	--	--	--	--	--
--	--	--	--	--	--	--	--
72	--	47	--	175	74	--	--
100	--	55	--	166	82	--	--
31	--	27	--	168	43	--	--
50	--	50	--	168	81	--	--
100	--	72	--	179	118	--	--
84	--	66	--	165	85	--	--
35	--	35	--	158	53	--	--
64	--	54	--	153	78	--	--
59	--	48	--	155	69	--	--
48	--	48	--	153	72	--	--
70	--	60	--	143	78	--	--
42	--	42	--	151	56	--	--
31	--	31	--	156	43	--	--
34	--	34	--	179	54	--	--
41	--	36	--	177	58	--	--
61	--	52	--	199	82	--	--
51	--	44	--	162	66	--	--
54	--	36	--	195	--	--	--
61	--	38	--	202	64	--	--
34	--	21	--	172	32	--	--
91	--	87	--	187	112	--	--

A download trace from a LIFEPAK 12 defibrillator, analysed using CODESTAT software (Physio Control). Time in minutes is shown on the left with each red bar representing a single chest compression. The trace demonstrates the cessation of chest compressions after 2 minutes to allow intubation, poor overall 'hands on the chest' time and a very rapid chest compression rate.

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Short communication

Resuscitation quality assurance for out-of-hospital cardiac arrest – Setting-up an ambulance defibrillator telemetry network

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Cardiac arrest

ABSTRACT

Background: Out of hospital cardiac arrest (OHCA) is a leading cause of pre-hospital mortality. Chest compressions performed during cardiopulmonary resuscitation aim to provide adequate perfusion to the vital organs during cardiac arrest. Poor resuscitation technique and the quality of pre hospital CPR influences outcome from OHCA. Transthoracic impedance (TTI) measurement is a useful tool in the assessment of the quality of pre hospital resuscitation by ambulance crews but TTI telemetry has not yet been performed in the United Kingdom. We describe a pilot study to implement a data network to collect defibrillator TTI data via telemetry from ambulances.

Methods: Prospective, observational pilot study over a 5 month period. Modems were fitted to 40 defibrillators on ambulances based in Edinburgh. TTI data was sent to a receiving computer after resuscitation attempts for OHCA.

Results: 58 TTI traces were transmitted during the pilot period. Compliance with the telemetry system was high. The mean ratio of chest compressions was 73% (95% CI 69–77%), the mean chest compression rate was 128 (95% CI 122–134). The mean time interval from chest compression interruption to shock delivery was 27 s (95% CI 22–32 s).

Conclusion: Trans thoracic impedance analysis is an effective means of recording important measures of resuscitation quality including the hands on the chest time, compression rate and defibrillation interval time. TTI data transmission via telemetry is straightforward, efficient and allows resuscitation data to be captured and analysed from a large geographical area. Further research is warranted on the impact of post-resuscitation reporting on the quality of resuscitation delivered by ambulance crews.

1. Background

Out-of-hospital cardiac arrest (OHCA) is one of the leading causes of mortality and serious neurological disability in Europe. Cardiopulmonary resuscitation (CPR) is vital to maintain cerebral and cardiac perfusion until return of spontaneous circulation (ROSC) can be achieved.

Several recent studies have reported the adverse physiological consequences of poor resuscitation technique[1] and have demonstrated that quality of pre-hospital CPR influences outcome from OHCA.[2,3]

Chest compressions aim to provide adequate perfusion to the vital organs during cardiac arrest. Periods during which chest compressions are not performed result in lack of blood flow – defined as no blood flow time (NBT). Recent clinical evidence shows increased NBT during CPR is associated with poor outcome.[2]

A variety of factors influence the delivery of effective chest compressions. Tracheal intubation and obtaining intravenous access for subsequent drug delivery interrupt chest compressions, but no high level evidence exists to show that either intervention improves survival from OHCA in humans.[4,5] Automated rhythm analysis will often take longer than manual rhythm interpretation by a trained healthcare professional, resulting in increased delay-to-shock times when ambulance defibrillators are used in automatic mode.[6,7]

Calculating the NBT has important implications for resuscitation training, optimising the quality of resuscitation and clinical outcome after OHCA.[8]

There have been calls for regular monitoring of CPR quality and for uniform reporting of CPR variables.[9] Ambulance crews receive initial training in performing CPR pre-hospital but receive variable training updates. Individual crews are likely to encounter

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few OHCA and skill retention can be problematic. There is a need to monitor compliance of CPR performed by ambulance crews in accordance with current international resuscitation guidelines,[10] as previous investigation of pre hospital practice has demonstrated poor compliance with recommended chest compression depth and rate, compounded by pauses in delivery of chest compressions.[11,12]

Determining the quality of pre-hospital resuscitation performed by ambulance crews in the field is technically difficult, but crucial if pre-hospital care of OHCA patients is to improve.[13]

Transthoracic impedance (TTI) measurement is a useful tool in the assessment of the quality of pre-hospital resuscitation by ambulance crews.[8,10] The TTI signal is already recorded through the pads of many models of external defibrillator without the need for any further equipment to be placed on the patient. Both chest compressions and ventilations result in identifiable changes in the TTI trace. Analysing the trace allows a variety of resuscitation metrics including the hands-on-the chest time, compression rate and time-to-shock intervals to be accurately measured.

Analysing the TTI trace from individual defibrillators following a resuscitation attempt requires the data to be downloaded to a computer, before analysis with software can occur. Data can be downloaded from the defibrillator using a direct cable connection or transmitted wirelessly via telemetry. The former requires the defibrillator to be taken to a download station post-resuscitation, is labour intensive, may delay ambulance crews returning to clinical duties and may result in a poor data capture rate. Sending the TTI data via telemetry allows more convenient data transmission post-resuscitation, which can be achieved directly from the ambulance and allows remote data access.

Logging and analysis of TTI data from ambulance defibrillators after OHCA does not yet occur routinely in the United Kingdom. We describe a pilot study to implement a data network to collect defibrillator TTI data via telemetry from ambulances in the City of Edinburgh, Scotland.

2. Methods

Ambulance crews in Scotland currently use the LIFEPAK 12 (Physio Control) defibrillator and transmit 12-lead electrocardiograph (ECG) data to Cardiology units using a low bandwidth telemetry system. The data file containing the TTI trace for each OHCA event was found to be significantly larger (500 kb – 3.5 MB) than a 12-lead ECG and transmitting such a large data file via telemetry was initially found to be problematic. Attempting to connect the defibrillator to a mobile telephone for data transmission via the existing Bluetooth system resulted in frequent signal fallout and unacceptably long (>20 min) data transmission times.

In our pilot project general packet radio service (GPRS) modems were fitted to 40 defibrillators on ambulances based at Edinburgh City Ambulance Station. This enabled faster, reliable data transmission. The modems were housed in a sealed case attached to the rear of the defibrillator and connected via serial cable. Operation of the modem was automatic and did not require any intervention by the ambulance crews.

Ambulance crews were informed via email and posters of the need to transmit the TTI trace following a resuscitation attempt and a sticker with detailed instructions was placed on each defibrillator as a reminder.

Following each resuscitation attempt, the attending ambulance crew selected the respective case and instructed the defibrillator to transmit the data. The TTI trace was typically transmitted in under 2 min using this technology. A choice of two different receiving targets was pre-configured on the defibrillator menu allowing transmission of a resuscitation attempt after OHCA or a 12-lead ECG in patients with suspected myocardial infarction as per the existing local protocol.

The TTI data packets are sent via GPRS and world-wide web to a LIFENET Server (Physio-Control). The LIFENET server then directs the data packet securely onwards to a receiving computer or multiple receiving destinations. No patient data is held on the server. To receive the TTI data, a computer with a permanent broadband internet connection is required. The data packet is stored and analysed using proprietary software (CODESTAT, Physio Control). The system can be configured to send an email notification to the study team on receipt of a TTI trace. The LIFENET system is a subscription service. The cost will vary depending on local mobile telephone operators but the approximate monthly cost is £30 per ambulance and £375 per hospital.

Importantly, we chose not to include patient-identifiable data in the transmission. Clinical data were matched probabilistically to the date and time of transmission and the individual defibrillator.

After receipt of the TTI trace, CODESTAT software was used to calculate the no-flow ratio, compression rate and time interval to administer defibrillatory shocks. A resuscitation report was generated that was printed and sent as part of feedback and training to the attending ambulance crew.

3. Results

During the initial pilot study period (1/11/2009 to 1/4/2010) 58 TTI traces were transmitted following OHCA. We found compliance with the system amongst ambulance crews to be high with many positive comments received on the usefulness of receiving post-resuscitation reports.

In two cases (3%), ambulance crews reported being initially unable to send the TTI data packet but when the ambulance moved location the data was sent successfully, indicating a region with poor GPRS signal as the likely cause of the failure.

All TTI traces were received and analysed on a single computer. During the study period, a hard drive error on the receiving computer resulted in permanent loss of data for 18 traces. Subsequently, a data back-up system was installed to protect against hardware failure.

From the initial 58 TTI traces received, the mean ratio of chest compressions was 73% (95% CI 69–77%), the mean chest compression rate was 128 (95% CI 122–134). There were 19 resuscitation attempts where at least once shock was administered from the defibrillator. The mean time interval from chest compression interruption to shock delivery was 27 s (95% CI 22–32 s)

4. Discussion

This is the first study to describe TTI telemetry in the United Kingdom. We found establishing a telemetry network to be an effective, time-efficient means of pre-hospital resuscitation data collection. Using GPRS technology to transmit TTI traces proved to be a reliable, rapid means of transmitting data to a remote computer for analysis. Data security and back-up is important to prevent loss of data in the event of a hardware failure.

Previous studies have highlighted the need to collect data on and monitor the quality of CPR performed by ambulance crews but few studies have described the methodology for collecting such data. Initial TTI data collected in our region has demonstrated the need to improve pre-hospital resuscitation practice.

A limitation of this pilot study was that we did not identify all OHCA cases attended by the modem-equipped ambulances during the study period to measure overall ambulance crew compliance with transmitting the traces.

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5. Conclusion

Evaluating quality of pre-hospital resuscitation practice is important to assure quality and to improve outcomes from OHCA. TTI analysis is an effective means of recording important measures of resuscitation quality including the hands-on-the-chest time, compression rate and defibrillation interval time. TTI data transmission via telemetry is straightforward, efficient and allows resuscitation data to be captured and analysed from a large geographical area. Further research is warranted on the impact of post-resuscitation reporting on the quality of resuscitation delivered by ambulance crews.

Conflict of interest statement

Dr. Lyon is supported by a Clinical Research Fellowship from Chest, Heart and Stroke Scotland. The modems and computer software used in this pilot study were supplied by Physio-Control. No funding was received for this study.

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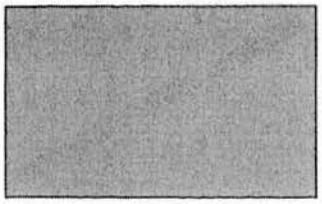
Appendix II - TOPCAT Data collection form

TOPCAT Data Collection Form

PATIENT DETAILS

Emergency Dept episode number ☐☐☐☐☐☐☐☐



Study number (to be completed by Investigator) ☐☐☐

Date D D / M M / Y Y

Lead Resuscitation care provider ☐☐☐☐☐

Sex (circle) **male** **female**

Study number (to be completed by Investigator) ☐☐☐

Investigator will complete ☐

INITIAL ASSESSMENT

In cardiac arrest on arrival to resuscitation (circle) **No** **Yes** ☐

If in arrest, presenting rhythm (circle) VF/ Pulseless VT /PEA/ Asystole / Agonal ☐

GCS on arrival E☐ M☐ V☐ ☐☐

Intubated pre-hospital (circle) **No** **Yes** ☐

ET tube in correct position on arrival in the ED (circle) **No** **Yes** ☐

Intubated/re-intubated in ED (circle) **No** **Yes** Bagged/ventilated in ED (circle) **No** **Yes** ☐☐

MANAGEMENT

Chest compressions performed (circle) **No** **Yes** ☐

If yes (circle): Manual LUCAS device ☐

Defibrillated in ED (circle) **No** **Yes** ☐

Number of DC shocks given ☐☐

Adrenaline given in ED (circle) **No** **Yes** ☐

Total in number of Mini-jets (mg) ☐☐

Any return of spontaneous circulation (ROSC) (circle) **No** **Yes**

Time of first ROSC H H : M M ☐

Any queries please contact Richard Lyon, bleep # 6461

TOPCAT Data Collection Form

Investigator will complete

PHYSIOLOGY

Temperature First tympanic temperature recording in °C ☐☐.☐ °C

First oesophageal temperature recording °C ☐☐.☐ °C

Was the patient actively cooled in the ED? (circle) **No** **Yes** ☐

Method (circle): ice packs cooling blanket cold saline ☐

Earliest gas result (circle): arterial venous ☐

pO2 ☐☐.☐ kPA pCO2 ☐☐.☐ kPA H+ ☐☐☐.☐ mmol

Bicarb ☐☐.☐ mmol Lactate ☐☐.☐

DISPOSAL

Date left the ED D D/M M/Y Y Time left the ED H H:M M ☐

Admitted to (circle) **ICU** **CCU** **Ward** **Mortuary**

Date of death D D/M M/Y Y Time of death H H:M M

Please place completed form in TOPCAT collection box in Resus.

THANK YOU

Any queries please contact Richard Lyon, bleep # 6461

Appendix III

Laboratory Protocols

Systemic inflammatory markers - laboratory protocol

All samples were stored at -80°C. Before analysis, samples were thawed to +4°C. Markers of systemic inflammation were measured in serum.

Materials included in the CBA kit

Human Inflammatory Cytokines Capture Beads (A1-6)

Wash buffer - 260ml bottle of phosphate buffered saline solution containing protein and detergent.

Assay diluent – a single, 30ml bottled of a buffered protein solution used to reconstitute and dilute the Human Inflammatory Cytokines Standards and to dilute test samples.

Serum Enhancement Buffer – A single, 10ml bottle of a buffered protein solution used to dilute mixed capture beads.

Human Inflammatory Cytokines PE detection Reagent (B)

Human Inflammatory Cytokines Standards (C)

PE Positive Control Detector

FITC Positive Control Detector

Materials required but not provided in kit

A flow cytometer equipped with a 488nm laser capable of detecting and distinguishing fluorescence emissions at 576 and 670 nm.

BD CBA software. The BD Cytometer was set and calibrated according to standard BD protocol (www.bdbiosciences.com)

Serum Assay Procedure

1. Mix 10ul/test of each Human Inflammatory Cytokine Capture Bead suspension (vortex briefly).
2. Pellet mixed beads by centrifugation and aspirate supernatant
3. Resuspend bead pellet in Serum Enhancement Buffer (equal volume to amount removed in step 2) and vortex briefly.

30 minute incubation at room temperature (protect from light)

4. Transfer 25 µl of mixed beads to each assay tube
5. Reconstitute Human Inflammatory Cytokine Standards in Assay Dilutent (15 min).

7. Add Standard Dilutions (from 1:1 serial dilutions by half to 1:256) and test samples to the appropriate sample tubes (25 µl/tube)

90 minute incubation at room temperature (protect from light)

8. Wash samples with 1ml Wash Buffer and centrifuge (leave approx 100µl residual volume after aspiration)
9. Add PE Detection Reagent (25µl/test)

10. Wash samples with 1ml Wash buffer and centrifuge.

11. Add 150µl of Wash buffer to each assay tube and analyse samples.

Neuron Specific Enolase Assay

Liaison NSE kit

A fully automated Liaison analyser (Diasorin, Italy) was used with an NSE module (Ref 314561) to assay for NSE in the TOPCAT serum samples.

Materials provided in the NSE kit:

Magnetic particle suspension (2.3ml): magnetic particles coated with anti-NSE, monoclonal (mouse)

Calibrator, low (1.5ml)

Calibrator, high (1.5ml)

Diluent (4ml)

Tracer conjugate (14ml): anti-NSE tracer, labelled with isoluminol, monoclonal (mouse)

Materials required but not provided:

Liaison Module (Ref 319130)

Liaison Starter Kit (Ref 319102)

Liaison Light Check (Ref 319101)

Liaison Wash/System Liquid (Ref 319100)

Liaison Waste Bags (Ref 450003)

Assay procedure

The Liaison Automated Analyser was configured according to the Analyser Operator's Manual. Liaison Calibration Solution was used to calibrate the NSE high and low levels. The Analyser operation was as follows:

25 µl TOPCAT serum sample
+ 20µl Coated magnetic particles
+ 100µl Tracer conjugate

10 min Incubation followed by a wash cycle
3s Measurement

S-100B Assay

Liaison S100 kit

A fully automated Liaison analyser (Diasorin, Italy) was used with an S100 module (Ref 314701) to assay for S100 in the TOPCAT serum samples.

Materials provided in the NSE kit:

Magnetic particle suspension (2.3ml): magnetic particles coated with anti-S100, monoclonal (mouse)

Assay buffer (14ml)

Tracer conjugate (23ml): anti-S100 tracer, labelled with isoluminol

Materials required but not provided:

Liaison Module (Ref 319130)

Liaison Starter Kit (Ref 319102)

Liaison Light Check (Ref 319101)

Liaison Wash/System Liquid (Ref 319100)

Liaison Waste Bags (Ref 450003)

Liaison S100 calibration (low/high) (Ref 319117)

Assay procedure

The Liaison Automated Analyser was configured according to the Analyser Operator's Manual. Liaison S100 Calibration Solution was used to calibrate the S100 high and low levels. The Analyser operation was as follows:

100 µl TOPCAT serum sample
+ 20µl Coated magnetic particles
+ 100µl Assay buffer

10 min Incubation followed by a wash cycle

+ 200µl Tracer conjugate

10 min Incubation followed by a wash cycle

3s Measurement

GFAP ELISA assay

All samples were stored at -80°C. Before analysis, samples were thawed to +4°C. GFAP was measured in serum.

ELISA protocol:

1. Samples were diluted 3x
2. A standard dilution curve was used (25ng/ml-0.25ng/ml)
3. 100µl of diluted Standards, Quality Controls, Standard Diluent and samples were pipetted, in duplicate, in wells pre-coated with polyclonal anti-human GFAP antibody.
4. The plate was incubated at 25°C for 2 hours, shaking at 300rpm on an orbital plate shaker.
5. The wells were washed 3-times
6. 100µl of Biotin Labelled Antibody solution was added to each well.
7. The plate was incubated at 25°C for 1 hour, shaking at 300rpm on an orbital plate shaker.
8. The wells were washed 3-times
9. 100µl of substrate solution was added into each well and the plate protected from light.
10. The plate was incubated for 15-miutes.
11. The colour development was stopped by adding 100µl of Stop Solution.
12. The absorbance of each well was determined using a microplate reader set to 450nm.

Neutrophil cell surface marker detection

Whole blood was stained for CD11b, CD64 and L-selectin (CD62L), using fluorophore conjugated murine monoclonal antibodies (Invitrogen, Paisley, UK). The fluorophores were R-phycoerythrin (RPE), tri-colour (TC) and fluorescein isothiocyanate (FITC) respectively. Murine IgG1 conjugated to the relevant fluorophore was used as an isotype control.

Antibody, or isotype control, was added to 50µl whole blood and incubated at 4°C for 30 minutes. The leucocytes were then fixed and erythrocytes lysed by the addition of 450µl of FACSlyse (BD Bioscience, Oxford, UK). Fixed cells were then analysed on a FACScan flow cytometer (BD Bioscience), and neutrophils gated by forward and side scatter characteristics. Previous confirmation of these gate positions was obtained using CD16 and CD14 stains to identify neutrophils and monocytes respectively (data not shown). Expression of the cell surface marker was measured as geometric mean fluorescence, using the arbitrary fluorescence intensity scale from the FACScan.

Appendix IV

Response Driver Training

Details of 3-day response driver training course.

Day 1	Cockpit drill Introductory drive Use of signals and handbrake Observations Hazards Driving plan Introduction to the driving system Steering
Day 2	Driving system (rural) Corners and bends Box overtaking Sustained rev gear changes Motorways Driving on ice/snow Night Driving The Law, exemptions, non-exemptions
Day 3	Emergency Driving Route planning Red mist Arriving at the scene Taking control / triage

Scottish Ambulance Service
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BETTER DRIVING COURSE
18TH – 20TH AUGUST 2008
Dr Richard Lyon
Specialty Registrar in Emergency Medicine
Pre-hospital Research Fellow

Introduction

As part of the 'Topcat' study in to core temperature of pre-hospital cardiac arrests, the Scottish Ambulance Service agreed to provide an intensive driving awareness course to Dr Richard Lyon, SpReg who is leading the study.
This course was predominately conducted in the car Dr Lyon will be using for the study.
The course, provided over three days, covered an introduction to systematic driving, heightened observations and hazard awareness. It was split in to three parts
Part 1: Urban driving
Part 2: Rural driving and skid avoidance.
Part 3: Emergency driving.

Report

Initially, Dr Lyon, presented as a competent driver who displayed a few bad habits that had developed over his years of driving. These included resting his foot on the clutch pedal and over use of the indicators.
He adapted his driving style quickly to include a systematic approach to the presented hazards. To achieve this, he developed his observation skills to obtain a greater all round view from the vehicle.
His existing steering technique was effective, but he adopted 'three pressure' braking which led to consistently smooth stopping procedures.
Whilst negotiating rural routes, Dr Lyon was introduced to cornering techniques. This improved his ability to read corners, using limit points and subsequently to maintain progress through corners without overuse of the brakes.
In addition, on day two, he attended a 2-hour skid avoidance course at Knockhill that covered cadence braking and how to correct all types of skids.
During the course, he was briefed about the exemptions and non-exemptions he can claim whilst conducting an emergency drive. He had the opportunity to attend emergency calls, which required driving on both urban and rural routes. This highlighted many teaching points with regard to the actions of other motorists.

The course also covered correct procedures to adopt on arrival at the scene and what to do if he was the first person on scene.

Conclusion

At the completion of the three days, Dr Lyon was using advanced observation skills to produce effective driving plans. This led to smooth, systematic drives being demonstrated with the emphasis on safety.

Neil Proven
Divisional Training Officer
South East Division
Scottish Ambulance Service

Appendix V

Equipment carried in TOPCAT response car

Airway and Breathing

Pocket mask

Portable suction unit

Oropharyngeal airways size 2,3,4

Nasopharyngeal airways sizes 6,7

Hudson mask with reservoir

Nebulizer mask

Bag-valve-mask with O_2 tubing

Laryngoscope with size 4 blade

Magill's forceps

Endotracheal tubes sizes 6,7,8,9

Laryngeal mask sizes 3,4,5

Circulation

Alcoswab

NaCl 0.9% 1000ml

Tourniquet

IV giving set

IV cannula 20G

IV cannula 18G

IV cannula 16G

IV cannula dressing

Multi trauma dressing

Medication - Oral

Paracetamol 500mg tabs

Ibuprofen 400 mg tabs

Co-codamol 30/500 tabs

Aspirin 300mg tabs

GTN spray

Cetirzine 10mg tabs

Oral glucose gel

Salbutamol inhaler

Prednisolone 5mg tabs

Medication - Intravenous

Midazolam 10mg/2ml

Morphine 10mg/ml

Diazepam 10mg/2ml

Adrenaline 1:1000 1ml

Naloxone 400mcg/ml

Chlorpheniramine 10mg/ml

Metoclopramide 10mg/2ml

Hydrocortisone 100mg/1ml

Ceftriaxone 1g

Benzylpenicillin 600mg

Rectal Diazepam 10mg

Glucose 50% 50ml

Adrenaline 1:10000 minijet

Atropine 3mg minijet

Sodium bicarbonate 8.4%

Syringes

Needles

Water for injection

NaCl 5ml ampoule

Additional Items

"D" size oxygen cylinder

Phillips FR2 semi-automatic defibrillator

Yellow clinical waste bags

Sharps box

Appendix VI

Ambulance crew perceptions of a pre-hospital doctor at the scene of out-of-hospital cardiac arrest

Question 1.

In the ambulance service, what is your primary role?		
Answer Options	Response Percent	Response Count
Paramedic	47.8%	22
Technician	45.7%	21
Paramedic Practitioner	2.2%	1
Lead Paramedic	2.2%	1
Officer	2.2%	1
Other (please specify)		4
answered question		46
skipped question		2

Question 2.

Have you worked with a doctor in the field before? (tick all that apply)		
Answer Options	Response Percent	Response Count
No	25.0%	12
Yes	58.3%	28
Medic One	60.4%	29
GP/BASICS doctor	54.2%	26
TOPCAT study/Dr R Lyon	33.3%	16
answered question		48
skipped question		0

Question 3.

At your recent call at which the TOPCAT doctor was present, was the emergency		
Answer Options	Response Percent	Response Count
Cardiac arrest	100.0%	48
Acute medical emergency	2.1%	1
Paediatric emergency	0.0%	0
Other (please specify)		0
answered question		48
skipped question		0

Question 4.

Please rate the following statements relating to your experience with the pre-hospital doctor. Please answer all statements.							
Answer Options	Strongly disagree (0)	Disagree (1)	Neutral (2)	Agree (3)	Strongly agree (4)	Rating Average	Response Count
The doctor was clearly identified	0	0	1	11	34	4.72	46
The doctor integrated well with the ambulance team	0	0	0	4	43	4.91	47
The doctor appeared comfortable in the field	0	0	0	4	42	4.91	46
I felt reassured by the doctor's presence	0	0	5	12	30	4.53	47
My own performance improved after the doctor arrived	1	5	25	9	7	3.34	47
The doctor's presence was intimidating	20	23	4	0	0	1.66	47
The doctor hindered my usual clinical work	25	18	2	0	2	1.64	47
The doctor performed useful clinical interventions	0	1	7	17	21	4.26	46
The doctor gave me useful feedback	0	0	3	19	25	4.47	47
					answered question		48
					skipped question		0

Question 5.

Overall, how do you rate the usefulness of having a doctor present at the call you were attending?		
Answer Options	Response Percent	Response Count
Very unhelpful	6.3%	3
Unhelpful	0.0%	0
Neutral	2.1%	1
Useful	27.1%	13
Very useful	64.6%	31
answered question		48
skipped question		0

Question 6.

If you found it useful having a doctor at the call you were attending please briefly say why.

Dr Lyons gave better understanding of unfolding events and has a far greater knoweledge from which to take from.

Ability to make clinical decissions without our protocols in the best interest of patient and family.
finding it difficult to cannulate pt,doctor cannulated pts neck to very good effect. doctor explained the importance of not stopping cpr ,and the statistics of stopping very breifly.the importance of core temp.

good to have someone with hospital intervention performance at the scene

I have had several experiences of this Doctor attending & have found each occassion to be beneficial not only to the patient but to myself & colleagues in way of learning different techniques & more specialised treatments or considerations.

Although the clinical procedures carried out during the incident were the same as we usually do, I feel that much more time was taken at the incident. We, as ambulance personnel, have a tendancy to 'load and go' so the patient can receive more definitive treatment by Doctors in the hospital environment. However, this incident taught me to allow myself time to carry out the skills I have. It also made me reconsider my CPR technique and that the quality, along with the time factor can be of GREAT benefit to the patient.

Giving us guidance in performing better cpr than we are currently taught to do.
expert advice and feedback on CPR technique.

Obese patient with a difficult airway, unable to intubate.
doctor able to gain i/v access and intubate patient

The patient was very large and the doctor assisted in getting a venflon in while working in a confined space.

It was useful because although it would have been futile to have transported our patient to hospital, we had no reason not to according to our JRCALC guidelines. Having a Doctor present to make that decision was very useful and the patiend was PLE'd on scene.

He was able to interprate to ECG during the arrest and advise us on the best time to move.

Having any extra medical professional is always helpful, even more so when that person is an expert in their field.

Always helpful to have greater medical expertise present at a cardiac arrest. Instead of simply following a set protocol there was opportunity for applying knowledge and learning during the event how to improve outcome for the patient.

Question 7.

Did the doctor perform any interventions that were outwith your usual protocol?

Answer Options	Response Percent	Response Count
No	31.3%	15
Yes	68.8%	33
Yes (please give details)		33
	answered question	**48**
	skipped question	**0**

Number	Yes (please give details)
1	temperature monitoring
	Administered Bicarb IV
2	Inserted Nasal thermometer
3	central line
4	administer drugs that paramedics/technicians don't carry.
5	stept out of paramedic guidlines for resusitation of astmatic arrest.ie 1,1000 im epinepherin and admin salbutamol.
6	Giving the patient drugs I am not authorised to use. Although a paramedic was present to administer certain drugs, doctors have a far wider range than the ambulance service.
7	Central line, discussion of continuation of care.
8	Central line
	Aministered bicarb
9	Nasal thermometer
10	topcat intervention
11	drugs and temperture taking
12	Temperature monitoring
13	central line
	Core temp
14	Central IV line
15	Doctor was willing to PLE patient at the scene, making it easier on the family as the patient had been in Cardiac Arrest for some time, when we would have had to transport within our protocols.
	Central line cannulation
16	core temperature monitoring
17	Gave more fluids than would be usual at this type of arrest
18	administration of 8 x 500ml saline fluid IV for hypovolaemia
19	cessation of resuscitation outside normal Sas parameters
20	canulated, intubated patient and administered cardiac drugs and fluids
21	CANULATION AND ADMINISTRATION OF DRUGS
22	A central line (IV) was in place.
23	A central line was in place, I have never seen this before and have just recently asked paramedics if they are able to do this.
24	cannulated pts neck to very good effect, return of spontanious pulse after small amount of cardiac drugs.pt made resp. effort enroute to hosp.
25	central line

26	A Line. Drug administration outwith Paramedic guide lines.
27	IV access was gained through the neck
28	cpr during shock load up and straight after delivering a shock when a patient has an output.
29	Higher emphasis on compressions, less on breaths. Greater use of manual mode on defibrillator
30	LMA. Paramedics are given training on the use of LMAs but we currently do not carry them.
31	doctor able to gain i/v access and intubate patient
32	Central Line
33	Simply encouraging more chest compressions - at every opportunity and in particular while the defib was charging before shocking.

Question 8.

Do you feel a skilled doctor working in the pre-hospital environment is		
Answer Options	Response Percent	Response Count
Never beneficial	0.0%	0
Rarely benefical	2.1%	1
Sometimes benefical	42.6%	20
Often beneficial	55.3%	26
answered question		47
skipped question		1

Question 9.

If you feel a doctor can be beneficial in the field, please indicate in which cases. (Please tick all that apply)		
Answer Options	Response Percent	Response Count
Major trauma	93.8%	45
Acute medical illness	41.7%	20
Paediatric emergencies	58.3%	28
Cardiac arrest	75.0%	36
Major incident	75.0%	36
answered question		48
skipped question		0

Question 10.

In dispatching a doctor to the scene, would you prefer (please tick all that apply)		
Answer Options	Response Percent	Response Count
Direct dispatch by Control	70.2%	33
Requested by on-scene crew	48.9%	23
answered question		47
skipped question		1

Number	Response Text
1	Unable to tick more than one strongly agree box on the survey.
2	The incident i was at Dr Lyons was very useful at the scene due to the nature of the job. A 22 year old female in cardiac arrest due to suspected OD.
3	The survey is very limited in its questioning and not all answers can be answered with a yes or no reply.In certain situations the experianced paramedic having worked with medic one or in the resuss room knowes what needs to be done in respect to drugs and treatment but has not got the authority or drugs to do what needs to be done
4	I think it will always be useful to have someone whose medical experience can bring increased patient care, as long as that presence does not hinder the safe removal and transportation of patient to a hospital environment.
5	Doctotrs would be more beneficial if there were no paramedics available.it would also depend on the sevrity of the case.
6	All though a doctor can somtimes be useful, I think it has to be remembered that paramedics are highly trained and very skillful in their own field. Although we are not doctors and hopefully no one ever tries to act like one, we do a very good job on our own and are not afraid to request help when required, medic one, for example. If doctors were to become a permanant feature in the out of hospital arena, ambulance crews would be relegated to taxi drivers, again. I think it should also be noted that as pro drivers, our skills are developed after our course has finished. Just completing an emergency driving course does not make you a safe and competent driver and you really do need to be driving every day at speed, to develop. As I said, when requested by ourselves, doctors in the field are a great help, often saving a life that would otherwise have been compromised if not lost. All I ask is that you let paramedics and technicians do their job while doctors do their's in hospitals and together the patient receives the best treatment from call to discharge.
7	Most GP's on scene are happy to take a 'back seat' and assist when requested. It is useful to have a pre hospital specialist on scene, but in the majority of cases there may be no need.
8	It is very difficult to ascertain the severity of a call on the phone, which would make it in-appropriate to dispatch a doctor to all apparent 'emergencies'. There is no easy way around this. In genuine cases a doctor could be beneficial if dispatched by control, as the time delay incurred waiting while on scene could prove detrimental to the patient's overall care, although there is no way to differentiate between real and apparent 'emergencies' from the initial call. So dispatch in ALL cases may not prove a good use of a valuable resourse.
9	edinburgh would greatly benefit from a joint paramedic and physician rapid repsonse vehicle
10	Dr Lyon is a credit to his profession,and works extremely well with the paramedics in the field.
11	Dr R Lyon is a very welcome clinical complement in my experiences of pre-hospital care within Edinburgh
12	I have answered Question 8 as cardiac arrest as this is my remit. I feel that a doctors' presence at all the named incidents must be an advantage
13	1) - The Doctor gave simple advice to Amb staff in relation to 'getting right back on to CPR' following a shock where there is a general Amb case of waiting a few seconds to look at the Defib Screen first. 2) - Can Paramedics place a central line as I have never seen it done before?
14	I would like to commend Dr Richard Lyons for not only his impressive knowledge & practical skills, but also for his ability to enter any enviroment & enhance the ongoing patient assessment/ treatment as part of the team. He is also to be commended for the time he takes with feedback, suggestions & advice when asked. My only suggestion to improve the service Dr Lyons brings to the pre-hospital setting would be for him to carry copious amounts of chocolate & orange Lucozade for the tired Paramedics.

15 I think the Topcat study is a great asset to Edinburgh. I feel I will benefit from the skills and experience a doctor bring to the calls. I will improve my skills at arrest because of this study. I look forward to taking part and find out more.
The only problem experienced related to who was ultimately 'in charge' of the scene. It was a fantastic learning experience to have a Topcat dr present and certainly improved treatment of the patient but logistics became awkward when ambulance staff were not sure of whether to proceed with basic scene control without checking first with the dr. This lead to an element of confusion that might be resolved simply by clarifying to all ambulance staff that once the dr is on scene the dr is ultimately in charge of all patient care. Otherwise, the scene can become confused and with no-one certain of their role.

16 Many thanks for all the Topcat feedback to ambulance staff - much appreciated both at station and in hospital.

Appendix VII

Study information sheets

PATIENT INFORMATION SHEET FOR TOPCAT STUDY

We appreciate this is a distressing time for you and your family. You are taking part in a research study after your heart stopped. You are being asked whether you want to remain in the study. Thank you for reading this information please read it carefully and take time to discuss it with your relatives.

What is the purpose of this study and why am I participating?

If the heart is restarted after a heart attack, cooling the body (therapeutic hypothermia) helps prevent brain damage and increases survival. The best method of therapeutic hypothermia is not known. We aim to gather information on your natural temperature after cardiac arrest and see what effect this has on vital chemical pathways in your body. This study involves collecting information only and does not alter your care in any way.

You have already been entered into the study after your cardiac arrest. We are asking whether you want to help us with this research and continue in the study. If you do *NOT* want to participate, you can be withdrawn from the study *AT ANY TIME*. You don't have to give a reason for not wanting to participate and this will not alter your care now or at any stage in the future.

We plan to look at body temperature and chemical pathways in the following ways:

1) **Simple blood tests taken before you arrived in hospital, during your stay in the Emergency Department and on up to three further occasions depending on your length of stay in hospital. When possible, blood tests will occur at the same time as routine clinical tests.**
2) **A small, soft, plastic thermometer placed in the back of the throat to measure body temperature for up to 24 hours.**

There are no unwanted side effects of having the thermometer and you will not have been aware of it.

With your agreement, we will telephone you 6 months after your discharge from hospital to ask you a few questions about your health.

If you do decide that you would want to continue to take part in this study we will ask you to sign a consent form. You will receive a copy of this information sheet and consent form.

All samples and other information collected about you during the course of this study will be kept strictly confidential and have your name and address removed so that they cannot be identified. Information will only be used by individuals directly involved in the research project. We also plan to store the samples and information that we gather at the Centre for Inflammation Research in the University of Edinburgh for possible use in future projects looking into heart diseases. We may wish to test the samples for genetic material after they have been anonymised but you can ask for this test not to occur if you wish. We will obtain formal ethical permission before conducting any further testing on the blood samples.

The study has been approved by the Local Research Ethics Committee.

Further information can be obtained from: Richard Lyon

Specialty Registrar in Emergency Medicine

Royal Infirmary, Edinburgh

0131 2421338

Thank you for your help

Dr Richard Lyon

RELATIVE INFORMATION SHEET FOR TOPCAT STUDY

We appreciate that this is a distressing time for you and your family. Your relative is taking part in a research study after their heart stopped. You are being invited to consider whether your relative would agree to take part. Thank you for reading this information, please read it carefully and take time to discuss it with your relatives.

What is the purpose of this study and why is my relative participating?

If the heart is restarted after a heart attack, cooling the body (therapeutic hypothermia) helps prevent brain damage and increases survival. The best method of therapeutic hypothermia is not known. We aim to gather information on the patients' temperature after cardiac arrest and see what effect this has on vital chemical pathways in the body. This study involves collecting information only and does not alter your relatives care in any way.

Your relative has already been provisionally entered into the study after their cardiac arrest. We have taken blood samples which have been frozen and not yet analysed. Your relatives' care has been not been affected in any way. We are asking you to consider whether your relative would want to help us with this research. If you feel they would *NOT* want to participate, they can we withdrawn *AT ANY TIME.* You don't have to give a reason for not wanting your relative to participate and this will not alter your relative's care, or your care, now or at any stage in the future.

In this study, we plan to look at body temperature and chemical pathways in the following ways:

1) **Simple blood tests taken before your relative arrived in hospital, during their stay in the Emergency Department and on up to three further occasions depending on their length of stay in hospital. When possible, blood tests will occur at the same time as routine clinical tests.**
2) **A small, soft, plastic thermometer placed at the back of the throat to measure body temperature for up to 24 hours.**

There are no unwanted side effects of having the thermometer and your relative will not be aware of it.

With your agreement, we will telephone your relative 6 months after their discharge from hospital to ask them a few questions about their health.

If you do decide that your relative would want to take part in this study we will ask you to sign a consent form. You will receive a copy of this information sheet and consent form to take away with you.

All samples and other information collected about your relative during the course of this study will be kept strictly confidential and have the name and address removed so that they cannot be identified. Information will only be used by individuals directly involved in the research project. We also plan to store the anonymous samples and information that we gather at the Centre for Inflammation Research at the University of Edinburgh, for possible use in future related research projects. We may wish to test the samples for genetic material after they have been anonymised but you can ask for this test not to occur if you wish. We will obtain formal ethical permission before conducting any further testing on the blood samples.

The study has been for approved by the Local Research Ethics Committee.

Further information can be obtained from: Richard Lyon

Specialty Registrar in Emergency Medicin

Royal Infirmary, Edinburgh

0131 2421338

Thank you for your help

Dr Richard Lyon

Appendix VIII

Consent forms

RELATIVE CONSENT FORM FOR TOPCAT STUDY

Principal Researcher: Dr Richard Lyon, Specialty Registrar in Emergency Medicine, Edinburgh.

I have read the information sheet for the above study. ○

I have had the opportunity to ask questions about the study and to discuss it with family and friends. ○

I understand the purpose of the study and how my relative will be involved.

I understand, and accept, that if my relative continues to takes part in the study they may not gain direct personal benefit from it. ○

I understand that all information collected in the study will be held in confidence and that, if published or presented, all my relative's personal details will be removed. ○

I give permission for the researchers to have access to my relative's medical notes and other routine NHS data sources when this is relevant to my relative taking part in the research. ○

I agree that my relative may be telephoned after discharge from hospital ○

I agree that the samples my relative provides and the information gathered from them may be stored by Dr Richard Lyon in the Centre for Inflammation Research at Edinburgh University for possible use in future projects. ○

I agree that the genetic material in the samples my relative gives may be studied after all personal details have been removed. ○

I confirm that I agree to my relative continuing to take part in the study, and I understand that I can request that they be withdrawn from it, at any time and for any reason without their medical care or legal rights being affected. ○

I agree for my relative to take part in the above study.

Patient taking part in study _____ Date: ___/ ___/ ___

Person taking consent: _____ Date: ___/ ___/ ___ Signature: _____

Relative of study participant.

Name:

Are you nearest relative, next-of-kin or welfare guardian? Yes, state relation:

No; no nearer relative is available. State relation:

Date: ___/ ___/ ___

Signature: _____

No relative or welfare guardian contactable ◯

Date: ___/ ___/ ___

RELATIVE CONSENT FORM FOR TOPCAT STUDY

Principal Researcher: Dr Richard Lyon, Specialty Registrar in Emergency Medicine, Edinburgh.

I have read the information sheet for the above study.

I have had the opportunity to ask questions about the study and to discuss it with family and friends. ◯

I understand the purpose of the study and how my relative will be involved. ◯

I understand, and accept, that if my relative continues to takes part in the study they may not gain direct personal benefit from it. ◯

I understand that all information collected in the study will be held in confidence and that, if published or presented, all my relative's personal details will be removed. ◯

I give permission for the researchers to have access to my relative's medical notes and other routine NHS data sources when this is relevant to my relative taking part in the research. ◯

I agree that my relative may be telephoned after discharge from hospital ◯

I agree that the samples my relative provides and the information gathered from them may be stored by Dr Richard Lyon in the Centre for Inflammation Research at Edinburgh University for possible use in future projects. ◯

I agree that the genetic material in the samples my relative gives may be studied after all personal details have been removed. ◯

I confirm that I agree to my relative continuing to take part in the study, and I understand that I can request that they be withdrawn from it, at any time and for any reason without their medical care or legal rights being affected. ◯

I agree for my relative to take part in the above study.

Patient taking part in study _____ Date: ___/ ___/ ___

Person taking consent: _____ Date: ___/ ___/ ___ Signature: _____

Relative of study participant.

Name:

Are you nearest relative, next-of-kin or welfare guardian?

Yes, state relation:

No; no nearer relative is available. State relation:

Date: ___/ ___/ ___

Signature: _____

No relative or welfare guardian contactable ◯

Date: ___/ ___/ __

Appendix - IX

OHCA management - Scottish Emergency Department survey

Questionnaire

1. Which NHS deanery do you primarily work in?
   - O NHS North
   - O NHS East
   - O NHS South-East
   - O NHS West

2. Which specialties do you primarily work in? (select all that apply)
   - O Emergency Medicine
   - O Intensive Therapy
   - O Anaesthetics
   - O Acute Medicine

3. What level of training are you?
   - O Consultant
   - O Specialist trainee
   - O Other

4. What type of hospital so you primarily work in?
   - O Teaching Hospital
   - O District General Hospital
   - O Community Hospital

5. How large is the hospital?
   - O 0 – 50 beds
   - O 50 – 250 beds
   - O 250 – 500 beds
   - O 500 – 750 beds
   - O 750 – 1000 beds
   - O 1000+ beds

6. How often do you admit patients following out-of-hospital cardiac arrest (OHCA)?
   - O Never
   - O Under 5 per year
   - O 5 – 10 per year
   - O 10 – 20 per year
   - O 20 – 50 per year
   - O 50+ per year

7. Does your hospital have access to primary PCI (Percutaneous Coronary Intervention) facilities?
   - O Yes, on-site access
   - O Yes, off-site access

- O No

8. When are these facilities available? (select all that apply)
   - O 24 hours/day
   - O 9 – 5 Mondays to Fridays
   - O Weekends
   - O Upon emergency request
   - O Facilities not available

9. Does your hospital have a protocol for the use of immediate PCI in OHCA patients?
   - O Yes
   - O No

10. What proportion of post-OHCA patients receive PCI?
    - O None
    - O < 10%
    - O 10 – 25%
    - O 25 – 50%
    - O 50 – 75%
    - O 75 – 90%
    - O > 90%

11. When are these patients sent for primary PCI?
    - O Prior to ED (Emergency Department) admission
    - O Upon transfer from ED to ITU (Intensive Therapy Unit)
    - O Shortly after admission onto ITU
    - O After discharge from ITU
    - O N/A (Not applicable)

12. Do you think post cardiac-arrest patients should be routinely sent for immediate coronary angiography?
    - O Yes
    - O No

13. What ECG features would trigger the decision to send the patient for immediate PCI? (select all that apply)
    - O Persistent ST elevation
    - O New LBBB
    - O Any ischaemic changes
    - O Decision not made on ECG features
    - O Other (please specify)

14. What Clinical features would trigger the decision to send the patient for immediate PCI? (select all that apply)
    - O Persistent hypotension
    - O Signs of LVF (left ventricular failure)
    - O High ionotrope requirement
    - O Absence of an obvious non-cardiac cause
    - O Decision not made on clinical features
    - O Other (please specify)

15. If PCI is not routinely used in OHCA patients, what reasons best describe why? (select all that apply)
    - O N/A

- O Facilities not available
- O No protocol for use
- O Insufficient evidence to support use
- O Difficulties in interpreting ECG changes
- O Unfavourable outcomes observed
- O Too few patients seen
- O Other (please specify)

16. Have you ever used Therapeutic Hypothermia (TH) in the Emergency Department, in a patient following out-of hospital cardiac arrest (OHCA)?
    - O Yes
    - O No

17. In what proportion of post-OHCA patients do you use TH, in the Emergency Department?
    - O None
    - O None, MTH initiated in the ITU
    - O < 10%
    - O 10 – 25%
    - O 25 – 50%
    - O 50 – 75%
    - O 75 – 90%
    - O > 90%

18. What are your views of the effectiveness of MTH in OHCA patients?
    - O Definitely effective
    - O Probably effective
    - O Indifferent
    - O Probably ineffective
    - O Definitely ineffective

19. Do you think it is practical to initiate MTH in the Emergency Department?
    - O Yes
    - O No

20. Is there a protocol in place in your hospital for MTH use in OHCA patients?
    - O Yes, in the ED
    - O Yes, in the ITU
    - O No

21. Where is MTH currently commenced in your hospital?
    - O Pre-hospital (ambulance)
    - O Emergency Department
    - O Intensive Therapy Unit
    - O TH not currently in use

22. Where do you think MTH should ideally be commenced?
    - O Pre-hospital (ambulance)
    - O Emergency Department
    - O Intensive Therapy Unit
    - O None

23. What method of cooling do you use? (select all that apply)
    - O Ice packs

- O Cold intravenous fluids
- O Cooling blankets
- O Intravenous cooling catheter
- O Cooling helmet
- O Lavage (pleural, peritoneal or gastric)
- O Wet towels + fanning
- O N/A
- O Other (please specify)

24. After return of spontaneous circulation, what is the usual length of time before cooling is initiated?
    - O less than 1 hour
    - O 1 – 2 hours
    - O 2 – 4 hours
    - O 4 – 6 hours
    - O 6+ hours
    - O N/A

25. When cooling, what temperature do you aim for?
    - O 30 – 32 degrees celsius
    - O 32 – 34 degrees celsius
    - O 34 – 36 degrees celsius
    - O N/A
    - O Other (please specify)
26. How long do you keep the patient cooled for?
    - O less than 6 hours
    - O 6 – 12 hours
    - O 12 – 24 hours
    - O 24 – 48 hours
    - O 48+ hours
    - O N/A

27. Would you cool OHCA patients following: (select all that apply)
    - O Ventricular Fibrillation arrest
    - O PEA arrest
    - O Pulseless VT arrest
    - O Asystolic arrest
    - O Traumatic cardiac arrest
    - O N/A

28. How do you re-warm patients?
    - O Passively
    - O Actively
    - O N/A

29. If you don't use MTH routinely for OHCA patients, what reasons best represent why? (select all that apply)
    - O N/A
    - O Equipment not available
    - O No protocol for use
    - O TH is commenced in the ITU instead
    - O Insufficient evidence for use
    - O Difficulties in practicality
    - O Too few patients seen
    - O Unfavourable outcomes observed

Appendix X

Log of calls to TOPCAT from Edinburgh EMDC

Date Call	Mobile	Arrived at Scene	AMPDS Despatch Code	Despatch Code Description
14 Aug 2008	11:46:44	11:53:46	31E01	Ineffective breathing
15 Aug 2008	10:26:00	10:35:30	29B04	Serious haemorrhage
17 Aug 2008	19:53:00	20:03:00	09E01	Not breathing at all
18 Aug 2008	11:35:34	11:41:30	29D02C	High Mechanism - Vehicle v pedestrian
20 Aug 2008	03:19:00	03:31:26	06C01	Abnormal Breathing
20 Aug 2008			17B01	Possibly Dangerous Body Area
20 Aug 2008			33C01	Not alert (acute change)
20 Aug 2008			06D01A	Severe Respiratory Distress - asthma
20 Aug 2008	13:24:12	13:41:15	31D01	Unconscious (at end of interrogation)
25 Aug 2008	14:09:00	14:24:00	09E01	Not breathing at all
27 Aug 2008	13:42:57	13:54:00	09E01	Not breathing at all
28 Aug 2008	08:03:34	08:20:00	09E01	Not breathing at all
28 Aug 2008	13:33:00	13:58:51	10D03	Clammy
30 Aug 2008	23:27:31	23:35:28	09E01	Not breathing at all
02 Sep 2008			09E01	Not breathing at all
02 Sep 2008	18:26:00	18:52:47	09E01	Not breathing at all
07 Sep 2008	10:29:58		31E01	Ineffective breathing
08 Sep 2008	20:56:02	21:11:00	09E01	Not breathing at all
10 Sep 2008	16:27:00	16:35:00	06D01	Severe Respiratory Distress
10 Sep 2008	21:45:29	22:08:52	09E01	Not breathing at all
15 Sep 2008	11:07:45		32B03	Unknown status
15 Sep 2008	18:15:39	18:19:17	09E01	Not breathing at all
16 Sep 2008	14:45:01	14:57:00	12D03	Irregular breathing
02 Oct 2008	16:09:00	16:12:39	09E01	Not breathing at all
04 Oct 2008	10:00:05	10:10:00	09E01	Not breathing at all
08 Oct 2008			09E01	Not breathing at all
08 Oct 2008	09:04:37	09:08:00	09E01	Not breathing at all
09 Oct 2008	06:21:07		09D01	Ineffective Breathing
09 Oct 2008	17:57:05	18:02:00	09E03	Hanging
12 Oct 2008			31D03	Not alert
12 Oct 2008	09:38:24	09:53:58	09E01	Not breathing at all
13 Oct 2008	06:37:46	06:49:27	09E01	Not breathing at all
13 Oct 2008	09:56:27		33C06	Emergency response req'd
13 Oct 2008				
15 Oct 2008	13:02:55	13:07:00	09E01	Not breathing at all
15 Oct 2008	14:34:40	14:46:04	09E01	Not breathing at all
16 Oct 2008	09:50:00	09:59:06	33D01	Susp cardiac or resp arrest
21 Oct 2008	08:49:24		09E01	Not breathing at all
23 Oct 2008	09:22:00		09E01	Not breathing at all
24 Oct 2008	13:12:48		09E01	Not breathing at all
24 Oct 2008	19:06:49		09E01	Not breathing at all
30 Oct 2008	13:37:52	13:54:26	09E01	Not breathing at all
31 Oct 2008			09E01	Not breathing at all
31 Oct 2008	09:12:13	09:18:00	09E01	Not breathing at all

04 Nov 2008	22:17:23	22:24:56	31D01	Unconscious (at end of interrogation)
08 Nov 2008	08:24:29	08:37:20	09E01	Not breathing at all
08 Nov 2008			33C02	Abnorm breathing(acute onset)
09 Nov 2008	06:37:09	06:48:08	09E01	Not breathing at all
09 Nov 2008	18:30:00	19:38:00	09E01	Not breathing at all
11 Nov 2008	08:47:36		09E01	Not breathing at all
11 Nov 2008	22:17:00	22:23:26	11E01	Choking verified/ineffective breath
25 Nov 2008			09B01	Obvious Death (unquestionable)
26 Nov 2008	14:43:58	14:49:40	31E01	Ineffective breathing
27 Nov 2008	10:27:32	10:34:08	09E01	Not breathing at all
27 Nov 2008	11:18:51	11:21:30	23O01A	Poisoning (without priority symptoms) - Accidental
27 Nov 2008	13:49:00	13:55:53	28C01	Not alert
30 Nov 2008	11:08:26	11:21:04	09E01	Not breathing at all
01 Dec 2008	09:46:00	09:58:43	09D01	Ineffective Breathing
17 Dec 2008	09:49:28	09:57:03	09E01	Not breathing at all
19 Dec 2008	20:10:20	20:20:00	09E02	Breathing Uncertain (Agonal)
30 Dec 2008	21:21:00	21:30:03	09E02	Breathing Uncertain (Agonal)
03 Jan 2009	17:07:00		09E01	Not breathing at all
05 Jan 2009	06:16:04	06:30:00	09E01	Not breathing at all
05 Jan 2009	08:30:05	08:37:38	17D04	Abnormal breathing
05 Jan 2009	12:58:52	13:14:00	09E03	Hanging
05 Jan 2009	18:01:57		09E01	Not breathing at all
05 Jan 2009	23:28:00	23:37:26	21B01	Possibly Dangerous Haemorrhage
09 Jan 2009	06:54:36	06:55:00	09D01	Ineffective Breathing
13 Jan 2009	15:32:00	15:36:00	09B01A	Obvious Death Unquestionable - Cold and stiff
13 Jan 2009	19:40:16	19:45:16	33C02	Abnorm breathing(acute onset)
15 Jan 2009	23:10:16	23:16:00	09E01	Not breathing at all
16 Jan 2009	09:42:04		09E01	Not breathing at all
19 Jan 2009	18:17:00	18:21:26	13D01	Unconscious
20 Jan 2009	08:43:00	08:53:26	09E01	Not breathing at all
20 Jan 2009	12:30:00	12:34:35	31D01	Unconscious (at end of interrogation)
26 Jan 2009	19:08:21		09E01	Not breathing at all
28 Jan 2009	21:16:37	21:30:47	23D01A	Unconscious - Accidental
28 Jan 2009	22:07:36	22:14:58	09E01	Not breathing at all
20 Feb 2009	17:50:07	17:56:00	29D04	Trapped victim
21 Feb 2009	10:11:47	10:22:17	31E01	Ineffective breathing
21 Feb 2009	12:44:02	12:56:22	31D01	Unconscious (at end of interrogation)
23 Feb 2009	11:46:41		09E01	Not breathing at all
28 Feb 2009	14:04:00	14:08:12	09B01A	Obvious Death Unquestionable - Cold and stiff
01 Mar 2009	13:45:48		09E01	Not breathing at all
03 Mar 2009	09:54:43	09:57:31	09E01	Not breathing at all
15 Mar 2009	19:29:10	19:36:45	06D01	Severe Respiratory Distress
16 Mar 2009	08:35:00	08:42:48	09E01	Not breathing at all
16 Mar 2009	11:17:50		09D01	Ineffective Breathing
16 Mar 2009	13:12:41		09E01	Not breathing at all
17 Mar 2009	05:47:12	05:55:07	09E01	Not breathing at all
17 Mar 2009	08:21:27	08:22:00	09B01A	Obvious Death Unquestionable - Cold and stiff
17 Mar 2009	09:34:05	09:42:23	31D01	Unconscious (at end of interrogation)
18 Mar 2009	08:01:00	08:18:43	09E01	Not breathing at all
18 Mar 2009	12:41:00	12:45:14	09E01	Not breathing at all
21 Mar 2009	02:25:54	02:26:00	07C01F	Building Fire persons reported inside - Fire
21 Mar 2009	17:32:22	17:34:59	09E01	Not breathing at all

27 Mar 2009	08:04:00	08:11:35	09B01A	Obvious Death Unquestionable - Cold and stiff
03 Apr 2009	12:43:00	12:58:45	09E01	Not breathing at all
06 Apr 2009	11:32:57	11:42:17	09E01	Not breathing at all
06 Apr 2009	13:13:40	13:17:39	09B01A	Obvious Death Unquestionable - Cold and stiff
06 Apr 2009	16:57:00	17:05:00	29D04	Trapped victim
07 Apr 2009	18:13:00	18:18:30	09E01	Not breathing at all
08 Apr 2009	13:19:00	13:25:11	09E01	Not breathing at all
09 Apr 2009	11:25:00	11:33:53	09E01	Not breathing at all
13 Apr 2009	20:37:07	20:42:15	09E01	Not breathing at all
16 Apr 2009	13:18:17	13:26:24	09E01	Not breathing at all
18 Apr 2009	12:44:24	12:50:06	09E01	Not breathing at all
18 Apr 2009	16:50:00	16:58:56	09E01	Not breathing at all
18 Apr 2009	17:48:29	18:00:39	09E01	Not breathing at all
19 Apr 2009			31D01	Unconscious (at end of interrogation)
28 Apr 2009	18:29:06	18:41:04	09E01	Not breathing at all
29 Apr 2009	10:13:32	10:21:24	09B01A	Obvious Death Unquestionable - Cold and stiff
01 May 2009	09:52:00	09:58:41	09E01	Not breathing at all
04 May 2009	11:44:09		09E01	Not breathing at all
04 May 2009	15:23:00	15:38:50	09E02	Breathing Uncertain (Agonal)
13 May 2009	17:21:11	18:58:58	09E01	Not breathing at all
18 May 2009	21:52:53	22:06:25	31E01	Ineffective breathing
26 May 2009	11:55:31	12:06:54	09E01	Not breathing at all
27 May 2009	19:49:28	19:59:04	09E01	Not breathing at all
01 Jun 2009	11:49:00	12:01:00	09E01	Not breathing at all
02 Jun 2009	10:37:00	10:41:03	09E02	Breathing Uncertain (Agonal)
02 Jun 2009			09E01	Not breathing at all
03 Jun 2009	08:05:00	08:11:38	09D01	Ineffective Breathing
03 Jun 2009	10:24:26	10:29:16	09E01	Not breathing at all
04 Jun 2009	13:28:35	13:45:22	12D03	Irregular breathing
05 Jun 2009	14:45:00	14:49:00	09E01	Not breathing at all
25 Jun 2009	09:27:29		09D01	Ineffective Breathing
25 Jun 2009	15:09:00	15:25:15	31E01	Ineffective breathing
25 Jun 2009	17:37:34	17:42:55	11E01	Choking verified/ineffective breath
26 Jun 2009			31D01	Unconscious (at end of interrogation)
27 Jun 2009	22:06:02	22:10:00	09E01	Not breathing at all
28 Jun 2009	22:00:00	22:08:16	31E01	Ineffective breathing
30 Jun 2009	11:01:00	11:10:37	09E01	Not breathing at all
02 Jul 2009	18:07:36	18:11:55	09E01	Not breathing at all
07 Jul 2009	06:56:00	07:05:23	09E01	Not breathing at all
08 Jul 2009	08:55:13		09E01	Not breathing at all
08 Jul 2009	11:58:00	12:11:59	09E01	Not breathing at all
09 Jul 2009	15:00:00	15:11:37	09E02	Breathing Uncertain (Agonal)
10 Jul 2009	10:35:45	10:41:00	19D01	Severe Respiratory Distress
11 Jul 2009	17:20:00	17:20:00	07C01F	Building Fire persons reported inside - Fire
14 Jul 2009	16:21:04	16:30:01	31D01	Unconscious (at end of interrogation)
17 Jul 2009	14:21:00	14:33:00	12D02E	Continuous/Multiple Fitting - Epileptic/Hist Fitt
21 Jul 2009	18:30:00	18:39:00	09E01	Not breathing at all
05 Aug 2009	09:27:55	09:40:22	31D01	Unconscious (at end of interrogation)
05 Aug 2009	11:00:35	11:14:26	31D01	Unconscious (at end of interrogation)
05 Aug 2009	13:23:04	13:37:48	09E01	Not breathing at all
10 Aug 2009	09:41:28	09:45:09	09E01	Not breathing at all
10 Aug 2009	13:04:24		31E01	Ineffective breathing

11 Aug 2009	20:46:11	20:51:00	09E01	Not breathing at all
12 Aug 2009	10:42:00	10:54:48	31E01	Ineffective breathing
12 Aug 2009	17:01:00	17:07:39	31D01	Unconscious (at end of interrogation)
13 Aug 2009	12:46:00	12:46:00	31E01	Ineffective breathing
13 Aug 2009	12:45:00	12:55:49	31E01	Ineffective breathing
20 Aug 2009	07:57:00	08:09:29	09E01	Not breathing at all
24 Aug 2009	12:19:00	12:23:44	09E01	Not breathing at all
26 Aug 2009	10:17:31	10:30:49	09E01	Not breathing at all
31 Aug 2009	14:35:00	14:43:11	31D01	Unconscious (at end of interrogation)
12 Sep 2009	13:15:22	13:15:22	29B06	Unknown Status
02 Oct 2009	09:03:00	09:10:29	09B01A	Obvious Death Unquestionable - Cold and stiff
04 Oct 2009	18:41:02	18:51:50	11E01	Choking verified/ineffective breath
06 Oct 2009			09E01	Not breathing at all
06 Oct 2009	21:17:23	21:21:00	06D01A	Severe Respiratory Distress - asthma
15 Oct 2009	22:30:50	22:42:29	09E02	Breathing Uncertain (Agonal)
17 Oct 2009			09E01	Not breathing at all
17 Oct 2009			09E01	Not breathing at all
18 Oct 2009			09E01	Not breathing at all
22 Oct 2009			09E02	Breathing Uncertain (Agonal)
23 Oct 2009	14:28:00	14:40:12	14D01	Unconscious
26 Oct 2009			09B01A	Obvious Death Unquestionable - Cold and stiff
28 Oct 2009	10:12:00		09D01	Ineffective Breathing
08 Nov 2009	16:14:00	16:15:59	12D03	Irregular breathing
14 Nov 2009	19:49:39	19:50:00	06D03	Clammy
26 Nov 2009	11:39:00	11:41:08	09D01	Ineffective Breathing
03 Dec 2009	10:03:09	10:10:44	09E03	Hanging
03 Dec 2009	15:17:00	15:29:21	12D02	Continuous or multiple fitting
06 Dec 2009			09B01A	Obvious Death Unquestionable - Cold and stiff
06 Dec 2009			26B01	Unknown Status
09 Dec 2009			33D01	Susp cardiac or resp arrest
26 Jan 2010	21:22:00		09E01	Not breathing at all
08 Feb 2010	20:13:00	20:26:00	09E01	Not breathing at all

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